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(54) **Title:** NOVEL PHOSPHINIC ACID-CONTAINING THYROMIMETICS

(57) **Abstract:** The present invention relates to compounds of phosphonic acid-containing T3 mimetics and monoesters thereof, stereoisomers, pharmaceutically acceptable salts, co-crystals, and prodrugs thereof and pharmaceutically acceptable salts and co-crystals of the prodrugs, as well as their preparation and uses for preventing and/or treating metabolic diseases such as obesity, NASH, hypercholesterolemia and hyperlipidemia, as well as associated conditions such as atherosclerosis, coronary heart disease, impaired glucose tolerance, metabolic syndrome x and diabetes.

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NOVEL PHOSPHINIC ACID-CONTAINING THYROMIMETICS

Cross-Reference to Related Applications

[0001] This application claims the benefit, under 35 U.S.C. § 119(e), of the earlier filing date of U.S. Provisional Application Nos. 60/684,573, filed May 26, 2005, and 60/725,169, filed October 6, 2005, the contents of which are incorporated by reference herein in their entirety, including figures.

Field of the Invention

[0002] The present invention is directed toward phosphinic acid-containing compounds that are thyroid receptor ligands, pharmaceutically acceptable salts, and to prodrugs of these compounds as well as their preparation and uses for preventing and/or treating metabolic diseases such as obesity, NASH, hypercholesterolemia and hyperlipidemia as well as associated conditions such as atherosclerosis, coronary heart disease, impaired glucose tolerance and diabetes. The invention is also related to the liver specific delivery of thyroid receptor ligands and the use of these compounds for the prevention and treatment of diseases responsive to modulation of T3-responsive genes in the liver.

Background of the Invention

[0003] The following description of the background is provided to aid in understanding, but is not admitted to be, or to describe, prior art. All publications and their cited references are incorporated by reference in their entirety.

[0004] Thyroid hormones (TH) are synthesized in the thyroid in response to thyroid stimulating hormone (TSH), which is secreted by the pituitary gland in response to various stimulants (*e.g.*, thyrotropin-releasing hormone (TRH) from the hypothalamus). Thyroid hormones are iodinated *O*-aryl tyrosine analogues excreted into the circulation primarily as 3,3',5,5'-tetraiodothyronine (T4). T4 is rapidly deiodinated in local tissues by thyroxine 5'-deiodinase to 3,3',5'-triiodothyronine (T3), which is the most potent TH. T3 is metabolized

to inactive metabolites via a variety of pathways, including pathways involving deiodination, glucuronidation, sulfation, deamination, and decarboxylation. Most of the circulating T4 and T3 is eliminated through the liver.

[0005] THs have profound physiological effects in animals and humans. Hyperthyroidism is associated with increased body temperature, general nervousness, weight loss despite increased appetite, muscle weakness and fatigue, increased bone resorption and enhanced calcification, and a variety of cardiovascular changes, including increased heart rate, increased stroke volume, increased cardiac index, cardiac hypertrophy, decreased peripheral vascular resistance, and increased pulse pressure. Hypothyroidism is generally associated with the opposite effects.

[0006] The biological activity of THs is mediated largely through thyroid hormone receptors (TRs). TRs belong to the nuclear receptor superfamily, which, along with its common partner, the retinoid X receptor, form heterodimers that act as ligand-inducible transcription factors. Like other nuclear receptors, TRs have a ligand binding domain and a DNA binding domain and regulate gene expression through ligand-dependent interactions with DNA response elements (thyroid response elements, TREs). Currently, the literature shows that TRs are encoded by two distinct genes (TRα and TRβ), which produce several isoforms through alternative splicing (Williams, *Mol. Cell Biol. 20(22)*:8329-42 (2000); Nagaya *et al., Biochem. Biophys. Res. Commun. 226(2)*:426-30 (1996)). The major isoforms that have so far been identified are TRα-1, TRα-2, TRβ-1 and TRβ-2. TRα-1 is ubiquitously expressed in the rat with highest expression in skeletal muscle and brown fat. TRβ-1 is also ubiquitously expressed with highest expression in the liver, brain and kidney. TRβ-2 is expressed in the anterior pituitary gland and specific regions of the hypothalamus as well as the developing brain and inner ear. In the rat and mouse liver, TRβ-1 is the predominant isoform (80%). The TR isoforms found in human and rat are highly homologous with respect to their amino acid sequences which suggest that each serves a specialized function.

[0007] TSH is an anterior pituitary hormone that regulates thyroid hormone production. TSH formation and secretion is in turn regulated by the hypothalamic thyrotropin releasing factor (TRH). TSH controls the uptake of iodide by the thyroid, the subsequent release of iodinated thyronines from thyroglobulin (*e.g.*, T3, T4) as well as possibly the intrapituitary conversion of circulating T4 to T3. Compounds that mimic T3 and T4 can negatively regulate both TSH and TRH secretion resulting in suppression of TSH levels and decreased levels of T3 and other iodinated thyronines. Negative regulation of TSH is postulated based on co-transfection and knockout studies (Abel *et al., J. Clin. Invest. 104*:291-300 (1999)) to arise through activation of the thyroid receptor TRβ, possibly the isoform TRβ-2, which is highly expressed in the pituitary.

[0008] The most widely recognized effects of THs are an increase in metabolic rate, oxygen consumption and heat production. T3 treatment increases oxygen consumption in isolated perfused liver and isolated hepatocytes. (Oh *et al., J. Nutr. 125(1)*:112-24 (1995); Oh *et al., Proc. Soc. Exp. Biol. Med. 207(3)*: 260-7 (1994)) Liver mitochondria from hyperthyroid rats exhibit increased oxygen consumption (Carreras *et al., Am. J. Physiol. Heart Circ. Physiol. 281(6)*:H2282-8 (2001) and higher activities of enzymes in the oxidative pathways (Dummler *et al., Biochem. J. 317(3)*:913-8 (1996), Schmehl *et al., FEBS Lett. 375(3)*:206-10 (1995), Harper *et al., Can. J. Physiol. Pharmacol. 72(8)*:899-908 (1994)). Conversely, mitochondria from hypothyroid rats show decreased oxygen consumption. Increased metabolic rates are associated with increased mitochondrial biogenesis and the associated 2- to 8-fold increase in mitochondrial mRNA levels. Some of the energy produced from the increased metabolic rate is captured as ATP (adenosine 5'-triphosphate), which is stored or used to drive biosynthetic pathways (*e.g.*, gluconeogenesis, lipogenesis, lipoprotein synthesis). Much of the energy, however, is lost in the form of heat (thermogenesis), which is associated with an increase in mitochondrial proton leak possibly arising from TH-mediated effects on mitochondrial membrane, uncoupling proteins, enzymes involved in the inefficient *sn*-glycerol 3-phosphate shuttle such as

mitochondrial *sn*-glycerol 3-phosphate dehydrogenase (mGPDH), and/or enzymes associated with proton leakage such as the adenine nucleotide transporter (ANT), Na^+/K^+-ATPase, Ca^{2+}-ATPase and ATP synthase.

[0009] THs also stimulate metabolism of cholesterol to bile acids. Hyperthyroidism leads to decreased plasma cholesterol levels, which is likely due to increased hepatic LDL receptor expression. Hypothyroidism is a well-established cause of hypercholesterolemia and elevated serum LDL. L-T3 is known to lower plasma cholesterol levels. The effects of T3 are attributed to TRβ since TRβ-deficient mice are resistant to T3-induced reduction in cholesterol levels. The effects on cholesterol levels have been postulated to result from direct effects on LDL receptor expression, enzymes involved in conversion of cholesterol to bile acids such as the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A) and/or possibly enzymes involved in cholesterol synthesis such as HMG CoA reductase. In addition, THs are known to affect levels of other lipoproteins linked to atherosclerosis. THs stimulate apo AI and the secretion of apo AI in HDL while reducing apo B100. Accordingly, one would expect T3 and T3 mimetics to inhibit the atherosclerotic process in the cholesterol fed animal.

[0010] THs simultaneously increase de novo fatty acid synthesis and oxidation through effects on enzymes such as ACC, FAS, and spot-14. THs increase circulating free fatty acids (FFA) levels in part by increasing production of FFAs from adipose tissue via TH-induced lipolysis. In addition, THs increase mitochondrial enzyme levels involved in FFA oxidation, *e.g.*, carnitine palmitoyltransferase 1 (CPT-1) and enzymes involved in energy storage and consumption.

[0011] The liver represents a major target organ of THs. Microarray analysis of hepatic gene expression from livers of hypothyroid mice and mice treated with T3 showed changes in mRNA levels for 55 genes (14 positively regulated and 41 negatively regulated) (Feng *et al., Mol. Endocrinol. 14(7)*: 947-55 (2000). Others have estimated that approximately 8% of the hepatic genes are regulated by T3. Many of these genes are important to both fatty acid and cholesterol synthesis and metabolism. T3 is also known to have other effects

in liver, including effects on carbohydrates through increased glycogenolysis and gluconeogenesis and decreased insulin action.

[0012] The heart is also a major target organ of THs. THs lower systemic vascular resistance, increase blood volume and produce inotropic and chronotropic effects. Overall TH results in increased cardiac output, which may suggest that T3 or T3 mimetics might be of use to treat patients with compromised cardiac function (*e.g.*, patients undergoing coronary artery bypass grafting (CABG) or cardiac arrest) (U.S. Patent No. 5,158,978). The changes in cardiac function are a result of changes in cardiac gene expression. Increased protein synthesis and increased cardiac organ weight are readily observed in T3-treated animals and represent the side effect of T3 that limits therapeutic use. TRβ knockout mice exhibit high TSH and T4 levels and increased heart rate suggesting that they retain cardiac sensitivity and therefore that the cardiac effects are via TRα. TRα knockouts exhibit reduced heart rates.

[0013] THs also play a role in the development and function of brown and white adipose tissue. Both TRα and TRβ are expressed in brown adipose tissue (BAT). THs induce differentiation of white adipose tissue (WAT) as well as a variety of lipogenic genes, including ACC, FAS, glucose-6-phosphate dehydrogenase and spot-14. Overall THs play an important role in regulating basal oxygen consumption, fat stores, lipogenesis and lipolysis (Oppenheimer *et al., J. Clin. Invest. 87(1)*:125-32 (1991)).

[0014] TH has been used as an antiobesity drug for over 50 years. In the 1940s TH was used alone, whereas in the 1950s it was used in combination with diuretics and in the 1960s in combination with amphetamines. Hyperthyroidism is associated with increased food intake but is also associated with an overall increase in the basal metabolic rate (BMR). Hyperthyroidism is also associated with decreased body weight (ca. 15%) whereas hypothyroidism is associated with a 25-30% increase in body weight. Treating hypothyroidism patients with T3 leads to a decrease in body weight for most patients but not all (17% of the patients maintain weight).

[0015] The effectiveness of TH treatment is complicated by the need for supraphysiological doses of T3 and the associated side effects, which include cardiac problems, muscle weakness and erosion of body mass. Long-term therapy has also been associated with bone loss. With these side effects, the medical community has tended to use thyroxine at low doses as an adjunct to dietary treatments. At these doses, TH has little effect on body weight or BMR.

[0016] The effectiveness of T3 to induce weight loss may be attenuated by defects in TH action. In comparison to normal animals, higher T3 doses were required in *ob/ob* mice to affect oxygen consumption, which was only observed in muscle, with no changes in liver and BAT. (Oh *et al., J. Nutr. 125(1)*:112-24 (1995); Oh *et al., Proc. Soc. Exp. Biol. Med. 207(3)*:260-7 (1994)). These effects were at least partially attributed to decreased uptake of T3 by the liver.

[0017] T3 analogues have been reported. Many were designed for use as cholesterol-lowering agents. Analogues that lower cholesterol and various lipoproteins (*e.g.*, LDL cholesterol and Lp(a)) without generating adverse cardiac effects have been reported (*e.g.*, Underwood *et al., Nature 324*:425-9 (1986)). In some cases the improved therapeutic profile is attributed to increased specificity for the TR-β wherein other cases it may be due to enhanced liver distribution. (Stanton *et al., Bioorg. Med. Chem. Lett. 10(15)*:1661-3 (2000); Dow *et al., Bioorg. Med. Chem. Lett. 13(3)*:379-82 (2003)).

[0018] T3 and T3 mimetics are thought to inhibit atherosclerosis by modulating the levels of certain lipoproteins known to be independent risk factors or potential risk factors of atherosclerosis, including low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, apoAI, which is a major apoprotein constituent of high density lipoprotein (HDL) particles and lipoprotein (a) or Lp (a).

[0019] Lp(a) is an important risk factor, elevated in many patients with premature atherosclerosis. Lp(a) is considered highly atherogenic (de Bruin *et al., J. Clin. Endocrinol. Metab. 76*:121-126 (1993)). In man, Lp(a) is a

hepatic acute phase protein that promotes the binding of LDL to cell surfaces independent of LDL receptors. Accordingly, Lp(a) is thought to provide supplementary cholesterol to certain cells, *e.g.*, cells involved in inflammation or repair. Lp(a) is an independent risk factor for premature atherosclerosis. Lp(a) is synthesized in the liver.

[0020] Apolipoprotein AI or apoAI is the major component of HDL, which is an independent risk factor of atherosclerosis. apoAI is thought to promote the efflux of cholesterol from peripheral tissues and higher levels of HDL (or apoAI) result in decreased risk of atherosclerosis.

[0021] Hyperthyroidism worsens glycemic control in type 2 diabetics. TH therapy is reported to stimulate hepatic gluconeogenesis. Enzymes specific to gluconeogenesis and important for controlling the pathway and its physiological role of producing glucose are known to be influenced by TH therapy. Phosphoenolpyruvate carboxykinase (PEPCK) is upregulated by TH (Park *et al, J. Biol. Chem. 274*:211 (1999)) whereas others have found that glucose 6-phosphatase is upregulated (Feng *et al., Mol. Endocrinol. 14*:947 (2000)). TH therapy is also associated with reduced glycogen levels.

[0022] TH therapy results in improved non insulin stimulated and insulin stimulated glucose utilization and decreased insulin resistance in the muscle of ob/ob mice. (Oh *et al., J. Nutr. 125*:125 (1995)).

[0023] There is still a need for novel thyromimetics that can be used to modulate cholesterol levels, to treat obesity, and other metabolic disorders especially with reduced undesirable effects.

Brief Description of the Drawings

[0024] Figure 1a depicts the binding of T3 to the TRα1 receptor using a homologous displacement reaction.

[0025] Figure 1b depicts the binding of T3 to the TRβ1 receptor using a homologous displacement reaction.

[0026] Figure 1c depicts the binding of Compound 17 to the TRα1 receptor using a heterologous displacement reaction.

[0027] Figure 1d depicts the binding of Compound 17 to the TRβ1 receptor using a heterologous displacement reaction.

[0028] Figure 1e depicts the binding of Compound 7 to the TRα1 receptor using a heterologous displacement reaction.

[0029] Figure 1f depicts the binding of Compound 7 to the TRβ1 receptor using a heterologous displacement reaction.

[0030] Figure 2a depicts the dose response of serum cholesterol levels to Compound 17 in cholesterol fed rats.

[0031] Figure 2b depicts the dose response of serum cholesterol levels to Compound 7 in cholesterol fed rats.

[0032] Figure 3a depicts the effect of Compound 17 on the weight of the heart in cholesterol fed rats.

[0033] Figure 3b depicts the effect of Compound 7 on the weight of the heart in cholesterol fed rats.

[0034] Figure 4a depicts the effect of Compound 17 on cardiac GPDH activity in cholesterol fed rats.

[0035] Figure 4b depicts the effect of Compound 7 on cardiac GPDH activity in cholesterol fed rats.

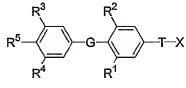
[0036] Figure 5 depicts the dose response of serum cholesterol levels to Compound 13-1-*cis* in cholesterol-fed rats.

Summary of the Invention

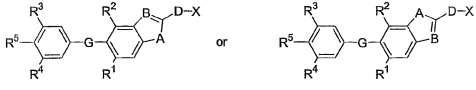
[0037] The present invention relates to phosphinic acid-containing compounds that bind to thyroid receptors in the liver. Activation of these receptors results in modulation of gene expression of genes regulated by thyroid hormones. The present invention also relates to pharmaceutically acceptable salts and co-crystals, prodrugs, and pharmaceutically acceptable salts and co-crystals of these prodrugs of these compounds. The compounds can be used to treat diseases and disorders including metabolic diseases. In one aspect, the phosphinic acid-containing compounds are useful for improving efficacy, improving the therapeutic index, *e.g.*, decreasing non-liver related toxicities

and side effects, or for improving liver selectivity, *i.e.*, increasing distribution of an active drug to the liver relative to extrahepatic tissues and more specifically increasing distribution of the an active drug to the nucleus of liver cells relative to the nucleus of extrahepatic tissue cells (including heart, kidney and pituitary). Prodrugs of the phosphinic acid-containing compounds are useful for increasing oral bioavailability and sustained delivery of the phosphorus-containing compounds.

[0038] In another aspect, the present invention relates to compounds of Formula I, II, III, VIII, X, XVI, and XVII. The compounds of Formula I, II, III, VIII, X, XVI, and XVII may be an active form or a prodrug thereof. Further included are pharmaceutically acceptable salts, including but not limited to acid addition salts and physiological salts, and co-crystals of said compounds of Formula I, II, III, VIII, X, XVI, and XVII. Further included in the present invention are prodrugs of compounds of Formula I, II, III, VIII, X, XVI, and XVII that are active forms, and pharmaceutically acceptable salts, including but not limited to acid addition salts and physiological salts, and co-crystals thereof. Further included are methods of making and using the compounds of the present invention.



Formula I



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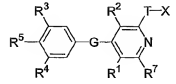

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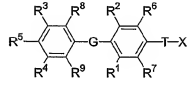
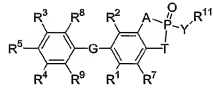


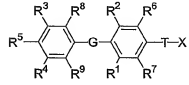
Formula VIII

(Ar^1)-G-(Ar^2)-T-X

Formula X



Formula XVI



Formula XVII

[0039] Some of the compounds of Formula I, II, III, VIII, X, XVI, and XVII have asymmetric centers. Thus included in the present invention are racemic mixtures, enantiomerically enriched mixtures, diastereomeric mixtures, including diastereomeric enriched mixtures, and individual stereoisomers of the compounds of Formula I, II, III, VIII, X, XVI, and XVII and prodrugs thereof.

Definitions

[0040] As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

[0041] T groups that have more than one atom are read from left to right wherein the left atom of the T group is connected to the phenyl group bearing the R^1 and R^2 groups, and the right atom of the T group is linked to the phosphorus atom in X. For example, when T is $-O-CH_2-$ or $-N(H)C(O)-$ it means -phenyl-$O-CH_2-P(O)YR^{11}Y'R^{11}$ and -phenyl-$N(H)C(O)-P(O)YR^{11}Y'R^{11}$.

[0042] The term "alkyl" refers to a straight or branched or cyclic chain hydrocarbon radical with only single carbon-carbon bonds. Representative examples include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *tert*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, and cyclohexyl, all of which may be optionally substituted. Alkyl groups are C_1-C_{20}.

[0043] The term "aryl" refers to aromatic groups which have 5-14 ring atoms and at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted.

[0044] Carbocyclic aryl groups are groups which have 6-14 ring atoms wherein the ring atoms on the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic carbocyclic aryl groups and polycyclic or fused compounds such as optionally substituted naphthyl groups.

[0045] Heterocyclic aryl or heteroaryl groups are groups which have 5-14 ring atoms wherein 1 to 4 heteroatoms are ring atoms in the aromatic ring and the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include

oxygen, sulfur, nitrogen, and selenium. Suitable heteroaryl groups include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolyl, pyridyl-N-oxide, pyrimidyl, pyrazinyl, imidazolyl, and the like, all optionally substituted.

[0046] The term "biaryl" represents aryl groups which have 5-14 atoms containing more than one aromatic ring including both fused ring systems and aryl groups substituted with other aryl groups. Such groups may be optionally substituted. Suitable biaryl groups include naphthyl and biphenyl.

[0047] The term "optionally substituted" or "substituted" includes groups substituted by one, two, three, four, five, or six substituents, independently selected from lower alkyl, lower aryl, lower aralkyl, lower cyclic alkyl, lower heterocycloalkyl, hydroxy, lower alkoxy, lower aryloxy, perhaloalkoxy, aralkoxy, lower heteroaryl, lower heteroaryloxy, lower heteroarylalkyl, lower heteroaralkoxy, azido, amino, halo, lower alkylthio, oxo, lower acylalkyl, lower carboxy esters, carboxyl, -carboxamido, nitro, lower acyloxy, lower aminoalkyl, lower alkylaminoaryl, lower alkylaryl, lower alkylaminoalkyl, lower alkoxyaryl, lower arylamino, lower aralkylamino, sulfonyl, lower -carboxamidoalkylaryl, lower -carboxamidoaryl, lower hydroxyalkyl, lower haloalkyl, lower alkylaminoalkylcarboxy-, lower aminocarboxamidoalkyl-, cyano, lower alkoxyalkyl, lower perhaloalkyl, and lower arylalkyloxyalkyl.

[0048] "Substituted aryl" and "substituted heteroaryl" refers to aryl and heteroaryl groups substituted with 1-3 substituents. These substituents are selected from the group consisting of lower alkyl, lower alkoxy, lower perhaloalkyl, halo, hydroxy, and amino.

[0049] The term "-aralkyl" refers to an alkylene group substituted with an aryl group. Suitable aralkyl groups include benzyl, picolyl, and the like, and may be optionally substituted. "Heteroarylalkyl" refers to an alkylene group substituted with a heteroaryl group.

[0050] The term "alkylaryl-" refers to an aryl group substituted with an alkyl group. "Lower alkylaryl-" refers to such groups where alkyl is lower alkyl.

[0051] The term "lower" referred to herein in connection with organic radicals or compounds respectively refers to 6 carbon atoms or less. Such groups may be straight chain, branched, or cyclic.

[0052] The term "higher" referred to herein in connection with organic radicals or compounds respectively refers to 7 carbon atoms or more. Such groups may be straight chain, branched, or cyclic.

[0053] The term "cyclic alkyl" or "cycloalkyl" refers to alkyl groups that are cyclic of 3 to 10 carbon atoms, and in one aspect are 3 to 6 carbon atoms Suitable cyclic groups include norbornyl and cyclopropyl. Such groups may be substituted.

[0054] The term "heterocyclic", "heterocyclic alkyl" or "heterocycloalkyl" refer to cyclic groups of 3 to 10 atoms, and in one aspect are 3 to 6 atoms, containing at least one heteroatom, in a further aspect are 1 to 3 heteroatoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Heterocyclic groups may be attached through a nitrogen or through a carbon atom in the ring. The heterocyclic alkyl groups include unsaturated cyclic, fused cyclic and spirocyclic groups. Suitable heterocyclic groups include pyrrolidinyl, morpholino, morpholinoethyl, and pyridyl.

[0055] The terms "arylamino" (a), and "aralkylamino" (b), respectively, refer to the group -NRR' wherein respectively, (a) R is aryl and R' is hydrogen, alkyl, aralkyl, heterocycloalkyl, or aryl, and (b) R is aralkyl and R' is hydrogen, aralkyl, aryl, alkyl or heterocycloalkyl.

[0056] The term "acyl" refers to -C(O)R where R is alkyl, heterocycloalkyl, or aryl.

[0057] The term "carboxy esters" refers to -C(O)OR where R is alkyl, aryl, aralkyl, cyclic alkyl, or heterocycloalkyl, all optionally substituted.

[0058] The term "carboxyl" refers to -C(O)OH.

[0059] The term "oxo" refers to =O in an alkyl or heterocycloalkyl group.

[0060] The term "amino" refers to -NRR' where R and R' are independently selected from hydrogen, alkyl, aryl, aralkyl and heterocycloalkyl, all except H are optionally substituted; and R and R' can form a cyclic ring system.

[0061] The term "-carboxylamido" refers to -$CONR_2$ where each R is independently hydrogen or alkyl.

[0062] The term "-sulphonylamido" or "-sulfonylamido" refers to $-S(=O)_2NR_2$ where each R is independently hydrogen or alkyl.

[0063] The term "halogen" or "halo" refers to -F, -Cl, -Br and -I.

[0064] The term "alkylaminoalkylcarboxy" refers to the group alkyl-NR-alk-C(O)-O- where "alk" is an alkylene group, and R is a H or lower alkyl.

[0065] The term "sulphonyl" or "sulfonyl" refers to $-SO_2R$, where R is H, alkyl, aryl, aralkyl, or heterocycloalkyl.

[0066] The term "sulphonate" or "sulfonate" refers to $-SO_2OR$, where R is -H, alkyl, aryl, aralkyl, or heterocycloalkyl.

[0067] The term "alkenyl" refers to unsaturated groups which have 2 to 12 atoms and contain at least one carbon-carbon double bond and includes straight-chain, branched-chain and cyclic groups. Alkenyl groups may be optionally substituted. Suitable alkenyl groups include allyl. "1-alkenyl" refers to alkenyl groups where the double bond is between the first and second carbon atom. If the 1-alkenyl group is attached to another group, *e.g.*, it is a W substituent attached to the cyclic phosphonate, it is attached at the first carbon.

[0068] The term "alkynyl" refers to unsaturated groups which have 2 to 12 atoms and contain at least one carbon-carbon triple bond and includes straight-chain, branched-chain and cyclic groups. Alkynyl groups may be optionally substituted. Suitable alkynyl groups include ethynyl. "1-alkynyl" refers to alkynyl groups where the triple bond is between the first and second carbon atom. If the 1-alkynyl group is attached to another group, *e.g.*, it is a W substituent attached to the cyclic phosphonate, it is attached at the first carbon.

[0069] The term "alkylene" refers to a divalent straight chain, branched chain or cyclic saturated aliphatic group. In one aspect the alkylene group contains up to and including 10 atoms. In another aspect the alkylene group contains up to and including 6 atoms. In a further aspect the alkylene group contains

up to and including 4 atoms. The alkylene group can be either straight, branched or cyclic.

[0070] The term "acyloxy" refers to the ester group -O-C(O)R, where R is H, alkyl, alkenyl, alkynyl, aryl, aralkyl, or heterocycloalkyl.

[0071] The term "aminoalkyl-" refers to the group NR_2-alk- wherein "alk" is an alkylene group and R is selected from -H, alkyl, aryl, aralkyl, and heterocycloalkyl.

[0072] The term "alkylaminoalkyl-" refers to the group alkyl-NR-alk- wherein each "alk" is an independently selected alkylene, and R is H or lower alkyl. "Lower alkylaminoalkyl-" refers to groups where the alkyl and the alkylene group is lower alkyl and alkylene, respectively.

[0073] The term "arylaminoalkyl-" refers to the group aryl-NR-alk- wherein "alk" is an alkylene group and R is -H, alkyl, aryl, aralkyl, or heterocycloalkyl. In "lower arylaminoalkyl-", the alkylene group is lower alkylene.

[0074] The term "alkylaminoaryl-" refers to the group alkyl-NR-aryl- wherein "aryl" is a divalent group and R is -H, alkyl, aralkyl, or heterocycloalkyl. In "lower alkylaminoaryl-", the alkyl group is lower alkyl.

[0075] The term "alkoxyaryl-" refers to an aryl group substituted with an alkyloxy group. In "lower alkyloxyaryl-," the alkyl group is lower alkyl.

[0076] The term "aryloxyalkyl-" refers to an alkyl group substituted with an aryloxy group.

[0077] The term "aralkyloxyalkyl-" refers to the group aryl-alk-O-alk- wherein "alk" is an alkylene group. "Lower aralkyloxyalkyl-" refers to such groups where the alkylene groups are lower alkylene.

[0078] The term "alkoxy-" or "alkyloxy-" refers to the group alkyl-O-.

[0079] The term "alkoxyalkyl-" or "alkyloxyalkyl-" refer to the group alkyl-O-alk- wherein "alk" is an alkylene group. In "lower alkoxyalkyl-," each alkyl and alkylene is lower alkyl and alkylene, respectively.

[0080] The term "alkylthio-" refers to the group alkyl-S-.

[0081] The term "alkylthioalkyl-" refers to the group alkyl-S-alk- wherein "alk" is an alkylene group. In "lower alkylthioalkyl-" each alkyl and alkylene is lower alkyl and alkylene, respectively.

[0082] The term "alkoxycarbonyloxy-" refers to alkyl-O-C(O)-O-.

[0083] The term "aryloxycarbonyloxy-" refers to aryl-O-C(O)-O-.

[0084] The term "alkylthiocarbonyloxy-" refers to alkyl-S-C(O)-O-.

[0085] The term "amido" refers to the NR_2 group next to an acyl or sulfonyl group as in NR_2-C(O)-, RC(O)-NR^1-, NR_2-S(=O)$_2$- and RS(=O)$_2$-NR^1-, where R and R^1 include -H, alkyl, aryl, aralkyl, and heterocycloalkyl.

[0086] The term "carboxamido" refer to NR_2-C(O)- and RC(O)-NR^1-, where R and R^1 include -H, alkyl, aryl, aralkyl, and heterocycloalkyl. The term does not include urea, -NR-C(O)-NR-.

[0087] The terms "sulphonamido" or "sulfonamido" refer to NR_2-S(=O)$_2$- and RS(=O)$_2$-NR^1-, where R and R^1 include -H, alkyl, aryl, aralkyl, and heterocycloalkyl. The term does not include sulfonylurea, -NR-S(=O)$_2$-NR-.

[0088] The term "carboxamidoalkylaryl" and "carboxamidoaryl" refers to an aryl-alk-NR^1-C(O), and ar-NR^1-C(O)-alk-, respectively where "ar" is aryl, "alk" is alkylene, R^1 and R include H, alkyl, aryl, aralkyl, and heterocycloalkyl.

[0089] The term "sulfonamidoalkylaryl" and "sulfonamidoaryl" refers to an aryl-alk-NR^1-S(=O)$_2$-, and ar-NR^1-S(=O)$_2$-, respectively where "ar" is aryl, "alk" is alkylene, R^1 and R include -H, alkyl, aryl, aralkyl, and heterocycloalkyl.

[0090] The term "hydroxyalkyl" refers to an alkyl group substituted with one -OH.

[0091] The term "haloalkyl" refers to an alkyl group substituted with halo.

[0092] The term "cyano" refers to $-C\equiv N$.

[0093] The term "nitro" refers to -NO_2.

[0094] The term "acylalkyl" refers to an alkyl-C(O)-alk-, where "alk" is alkylene.

[0095] The term "aminocarboxamidoalkyl-" refers to the group NR_2-C(O)-N(R)-alk- wherein R is an alkyl group or H and "alk" is an alkylene group. "Lower aminocarboxamidoalkyl-" refers to such groups wherein "alk" is lower alkylene.

[0096] The term "heteroarylalkyl" refers to an alkylene group substituted with a heteroaryl group.

[0097] The term "perhalo" refers to groups wherein every C-H bond has been replaced with a C-halo bond on an aliphatic or aryl group. Suitable perhaloalkyl groups include $-CF_3$ and $-CFCl_2$.

[0098] The term "carboxylic acid moiety" refers to a compound having a carboxylic acid group (-COOH), and salts thereof, a carboxylic acid ester, or a carboxylic acid surrogate.

[0099] The term "surrogates of carboxylic acid" refers to groups that possess near equal molecular shapes and volumes as carboxylic acid and which exhibit similar physical and biological properties. Examples of surrogates of carboxylic acid include, but are not limited to, tetrazole, 6-azauracil, acylsulphonamides, sulphonates, thiazolidinedione, hydroxamic acid, oxamic acid, malonamic acid, and carboxylic acid amides. Because phosphorus-containing thyromimetics (*e.g.*, phosphonic acid-, phosphonic acid monoester-, and phosphinic acid-containing compounds) have a markedly different biological activity as compared to carboxylic acid-containing thyromimetics, phosphonic acid, phosphonic acid monoester, and phosphinic acid are not considered to be surrogates of carboxylic acid in these compounds.

[0100] The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion. The co-crystals of the present invention comprise a co-crystal former H-bonded to a compound of the present invention. The co-crystal former may be H-bonded directly to the compound of the present invention or may be H-bonded to an additional molecule which is bound to the compound of the present invention. The additional molecule may be H-bonded to the compound of the present invention or bound ionically to the compound of the present invention. The additional molecule could also be a second API. Solvates of compounds of the present invention that do not further comprise a co-crystal former are not "co-crystals" according to the present invention. The

co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention as a co-crystal.

[0101] The co-crystals may also be a co-crystal between a co-crystal former and a salt of a compound of the present invention, but the compound of the present invention and the co-crystal former are constructed or bonded together through hydrogen bonds. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other.

[0102] Crystalline material comprised of solid compound of the present invention and one or more liquid solvents (at room temperature) are included in the present invention as "solvates." A "hydrate" is where the solvent is water. Other forms of the present invention include, but are not limited to, anhydrous forms and de-solvated solvates.

[0103] The ratio of the compound of the present invention to co-crystal former or solvent may be specified as stoichiometric or non-stoichiometric. 1:1, 1.5:1, 1:1.5, 2:1, 1:2, and 1:3 ratios of API:co-crystal former/solvent are examples of stoichiometric ratios.

[0104] The term "binding" means the specific association of the compound of interest to the thyroid hormone receptor. One method of measuring binding in this invention is the ability of the compound to inhibit the association of ^{125}I-T3 with a mixture of thyroid hormone receptors using nuclear extracts or purified or partially purified thyroid hormone receptor (for example, alpha or beta) in a heterologous assay.

[0105] The term "energy expenditure" means basal or resting metabolic rate as defined by Schoeller *et al., J Appl Physiol. 53(4):955-9* (1982). Increases

in the resting metabolic rate can be also be measured using increases in O_2 consumption and/or CO_2 efflux and/or increases in organ or body temperature.

[0106] The phrase "therapeutically effective amount" means an amount of a compound or a combination of compounds that ameliorates, attenuates or eliminates one or more of the symptoms of a particular disease or condition or prevents, modifies, or delays the onset of one or more of the symptoms of a particular disease or condition.

[0107] The term "pharmaceutically acceptable salt" includes salts of compounds of Formula I and its prodrugs derived from the combination of a compound of this invention and an organic or inorganic acid or base. Suitable acids include acetic acid, adipic acid, benzenesulfonic acid, (+)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic acid, citric acid, 1,2-ethanedisulfonic acid, dodecyl sulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glucuronic acid, hippuric acid, hydrochloride hemiethanolic acid, HBr, HCl, HI, 2-hydroxyethanesulfonic acid, lactic acid, lactobionic acid, maleic acid, methanesulfonic acid, methylbromide acid, methyl sulfuric acid, 2-naphthalenesulfonic acid, nitric acid, oleic acid, 4,4'-methylenebis [3-hydroxy-2-naphthalenecarboxylic acid], phosphoric acid, polygalacturonic acid, stearic acid, succinic acid, sulfuric acid, sulfosalicylic acid, tannic acid, tartaric acid, terphthalic acid, and *p*-toluenesulfonic acid.

[0108] The term "patient" means an animal.

[0109] The term "animal" includes birds and mammals. In one embodiment a mammal includes a dog, cat, cow, horse, goat, sheep, pig or human. In one embodiment the animal is a human. In another embodiment the animal is a male. In another embodiment the animal is a female.

[0110] The term "prodrug" as used herein refers to any compound that when administered to a biological system generates a biologically active compound as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination of each. Standard prodrugs are formed using groups attached to functionality, *e.g.*, HO-, HS-, HOOC-, R_2N-, associated with the drug, that cleave *in vivo*.

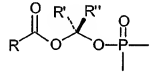
Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. The groups illustrated are exemplary, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Such prodrugs of the compounds of the present invention fall within this scope. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active or is a precursor of the biologically active compound. In some cases, the prodrug is biologically active, usually less than the drug itself, and serves to improve drug efficacy or safety through improved oral bioavailability, and/or pharmacodynamic half-life, etc. Prodrug forms of compounds may be utilized, for example, to improve bioavailability, improve subject acceptability such as by masking or reducing unpleasant characteristics such as bitter taste or gastrointestinal irritability, alter solubility such as for intravenous use, provide for prolonged or sustained release or delivery, improve ease of formulation, or provide site-specific delivery of the compound. Prodrugs are described in The Organic Chemistry of Drug Design and Drug Action, by Richard B. Silverman, Academic Press, San Diego, 1992. Chapter 8: "Prodrugs and Drug delivery Systems" pp.352-401; Design of Prodrugs, edited by H. Bundgaard, Elsevier Science, Amsterdam, 1985; Design of Biopharmaceutical Properties through Prodrugs and Analogs, Ed. by E. B. Roche, American Pharmaceutical Association, Washington, 1977; and Drug Delivery Systems, ed. by R. L. Juliano, Oxford Univ. Press, Oxford, 1980.

[0111] The term "phosphinate prodrug" refers to compounds that breakdown chemically or enzymatically to a phosphinic acid group *in vivo*. As employed herein the term includes, but is not limited to, the following groups and combinations of these groups:

[0112] Acyloxyalkyl esters which are well described in the literature (Farquhar *et al., J. Pharm. Sci. 72*:324-325 (1983)).

[0113] Other acyloxyalkyl esters are possible in which a cyclic alkyl ring is formed. These esters have been shown to generate phosphorus-containing nucleotides inside cells through a postulated sequence of reactions beginning with deesterification and followed by a series of elimination reactions (*e.g.*, Freed *et al., Biochem. Pharm, 38*:3193-3198 (1989)).

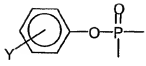
[0114] Another class of these double esters known as alkyloxycarbonyloxymethyl esters, as shown in formula A, where R is alkoxy, aryloxy, alkylthio, arylthio, alkylamino, and arylamino; R', and R" are independently -H, alkyl, aryl, alkylaryl, and heterocycloalkyl have been studied in the area of β-lactam antibiotics (Nishimura *et al., J. Antibiotics 40(1)*:81-90 (1987); for a review see Ferres, H., *Drugs of Today, 19*:499 (1983)). More recently Cathy, M. S. *et al.* (Abstract from AAPS Western Regional Meeting, April, 1997) showed that these alkyloxycarbonyloxymethyl ester prodrugs on (9-[(R)-2-phosphonomethoxy)propyl]adenine (PMPA) are bioavailable up to 30% in dogs.



Formula A

wherein R, R', and R" are independently H, alkyl, aryl, alkylaryl, and alicyclic (see WO 90/08155; WO 90/10636).

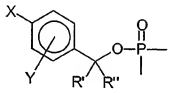
[0115] Aryl esters have also been used as prodrugs (*e.g.*, DeLambert *et al., J. Med. Chem. 37(7)*:498-511 (1994); Serafinowska *et al., J. Med. Chem. 38(8)*:1372-9 (1995). Phenyl as well as mono and poly-substituted phenyl proesters have generated the parent phosphonic acid in studies conducted in animals and in man (Formula B). Another approach has been described where Y is a carboxylic ester ortho to the phosphate (Khamnei *et al., J. Med. Chem. 39*:4109-15 (1996)).



Formula B

wherein Y is -H, alkyl, aryl, alkylaryl, alkoxy, acyloxy, halogen, amino, alkoxycarbonyl, hydroxy, cyano, and heterocycloalkyl.

[0116] Benzyl esters have also been reported to generate the parent phosphinic acid. In some cases, using substituents at the *para*-position can accelerate the hydrolysis. Benzyl analogs with 4-acyloxy or 4-alkyloxy group [Formula C, X = -H, OR or O(CO)R or O(CO)OR] can generate the 4-hydroxy compound more readily through the action of enzymes, *e.g.*, oxidases, esterases, etc. Examples of this class of prodrugs are described in Mitchell *et al., J. Chem. Soc. Perkin Trans. I* 2345 (1992); WO 91/19721.



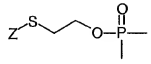
Formula C

wherein X and Y are independently -H, alkyl, aryl, alkylaryl, alkoxy, acyloxy, hydroxy, cyano, nitro, perhaloalkyl, halo, or alkyloxycarbonyl; and

R' and R'' are independently -H, alkyl, aryl, alkylaryl, halogen, and cyclic alkyl.

[0117] Thio-containing phosphinate proesters may also be useful in the delivery of drugs to hepatocytes. These proesters contain a protected thioethyl moiety as shown in formula D. Since the mechanism that results in de-esterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the disulfide is reduced by a reductase-mediated process (Puech *et al., Antiviral Res. 22*:155-174 (1993)).

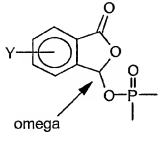
Thioesters will also generate free thiolates after esterase-mediated hydrolysis Benzaria, *et al., J. Med. Chem. 39(25):*4958-65 (1996)).

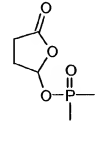


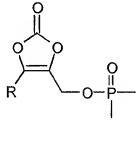
Formula D

wherein Z is alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, or alkylthio.

[0118] Other examples of suitable prodrugs include proester classes exemplified by Biller and Magnin (U.S. Patent No. 5,157,027); Serafinowska *et al., J. Med. Chem. 38(8):*1372-9 (1995); Starrett *et al., J. Med. Chem. 37:*1857 (1994); Martin *et al. J. Pharm. Sci. 76:*180 (1987); Alexander *et al., Collect. Czech. Chem. Commun. 59:*1853 (1994); and EP 0 632 048 A1. Some of the structural classes described are optionally substituted, including fused lactones attached at the omega position (formulae D-1 and D-2) and optionally substituted 2-oxo-1,3-dioxolenes attached through a methylene to the phosphorus oxygen (formula D-3) such as:







3-phthalidyl 2-oxotetrahydrofuran-5-yl 2-oxo-4,5-didehydro-1,3-dioxolanemethyl

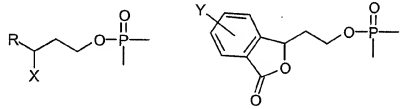
D-1 **D-2** **D-3**

wherein R is -H, alkyl, cycloalkyl, or heterocycloalkyl; and

wherein Y is -H, alkyl, aryl, alkylaryl, cyano, alkoxy, acyloxy, halogen, amino, heterocycloalkyl, and alkoxycarbonyl.

[0119] The prodrugs of Formula D-3 are an example of "optionally substituted heterocycloalkyl where the cyclic moiety contains a carbonate or thiocarbonate."

[0120] Propyl phosphinate proesters can also be used to deliver drugs into hepatocytes. These proesters may contain a hydroxyl and hydroxyl group derivatives at the 3-position of the propyl group as shown in formula E. The R and X groups can form a cyclic ring system as shown in formula E.



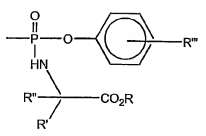
Formula E

wherein R is alkyl, aryl, heteroaryl;

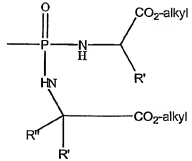
X is hydrogen, alkylcarbonyloxy, alkyloxycarbonyloxy; and

Y is alkyl, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, halogen, hydrogen, hydroxy, acyloxy, amino.

[0121] Phosphoramidate derivatives have been explored as phosphate prodrugs (*e.g.,* McGuigan *et al., J. Med. Chem. 42*:393 (1999) and references cited therein) as shown in Formula F and G.



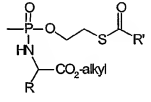
Formula F



Formula G

[0122] Cyclic phosphoramidates have also been studied as phosphonate prodrugs because of their speculated higher stability compared to non-cyclic phosphoramidates *(e.g.,* Starrett *et al., J. Med. Chem. 37*:1857 (1994)).

[0123] Another type of phosphoramidate prodrug was reported as the combination of S-acyl-2-thioethyl ester and phosphoramidate (Egron *et al., Nucleosides Nucleotides 18*:981 (1999)) as shown in Formula H:

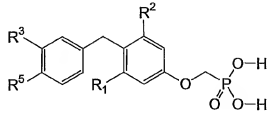


Formula H

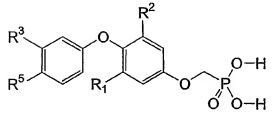
[0124] Other prodrugs are possible based on literature reports such as substituted ethyls, for example, bis(trichloroethyl)esters as disclosed by McGuigan, *et al., Bioorg Med. Chem. Lett. 3*:1207-1210 (1993), and the phenyl and benzyl combined nucleotide esters reported by Meier, C. *et al., Bioorg. Med. Chem. Lett. 7*:99-104 (1997).

[0125] The naming of the compounds is done by having the ring bearing the groups R^5 and R^3 be a substituent on the ring bearing the R^1 and R^2 groups. The naming of the prodrugs is done by having the diaryl system with its linker T (Formula I, III, VIII, XVI, or XVII) or D (Formula II) be a substituent on the phosphorus atom contained in X. For example:

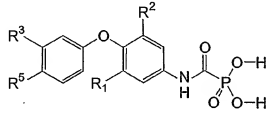
[3-R^1-5-R^2-4-(4'-R^5-3'-R^3-benzyl)phenoxy]methylphosphonic acid represents the formula:



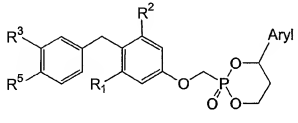
[3-R^1-5-R^2-4-(4'-R^5-3'-R^3-phenoxy)phenoxy]methylphosphonic acid represents the formula:



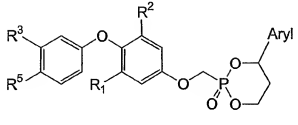
N-[3-R^1-5-R^2-4-(4'-R^5-3'-R^3-phenoxy)phenyl]carbamoylphosphonic acid represents the formula:



2-[(3-R^1-5-R^2-4-(4'-R^5-3'-R^3-benzyl)phenoxy)methyl]-4-aryl-2-oxo-2λ^5-[1,3,2]-dioxaphosphonane:



2-[(3-R^1-5-R^2-4-(4'-R^5-3'-R^3-phenoxy)phenoxy)methyl]-4-aryl-2-oxo-2λ^5-[1,3,2]-dioxaphosphonane:



[0126] The term "percent enantiomeric excess (% ee)" refers to optical purity. It is obtained by using the following formula:

$$\frac{[R] - [S]}{[R] + [S]} \times 100 = \%R - \%S$$

where [R] is the amount of the R isomer and [S] is the amount of the S isomer. This formula provides the % ee when R is the dominant isomer.

[0127] The term "enantioenriched" or "enantiomerically enriched" refers to a sample of a chiral compound that consists of more of one enantiomer than the other. The extent to which a sample is enantiomerically enriched is quantitated by the enantiomeric ratio or the enantiomeric excess.

[0128] The term "liver" refers to liver organ.

[0129] The term "enhancing" refers to increasing or improving a specific property.

[0130] The term "liver specificity" refers to the ratio:

$$\frac{[\text{drug or a drug metabolite in liver tissue}]}{[\text{drug or a drug metabolite in blood or another tissue}]}$$

as measured in animals treated with the drug or a prodrug. The ratio can be determined by measuring tissue levels at a specific time or may represent an AUC based on values measured at three or more time points.

[0131] The term "phosphorus-containing compounds" refers to compounds that contain PO_3H_2, PO_3^{-2}, PO_2HR, PO_2R^{-1}, and monoesters thereof.

[0132] The term "inhibitor of fructose-1,6-biphosphatase" or "FBPase inhibitor" refers to compounds that inhibit FBPase enzyme activity and thereby block the conversion of fructose 1,6-bisphosphate, the substrate of the enzyme, to fructose 6-phosphate. These compounds have an IC_{50} of equal to or less than 50 μM on human liver FBPase measured according to the procedure found in US 6,489,476.

[0133] The term "increased or enhanced liver specificity" refers to an increase in the liver specificity ratio in animals treated with a compound of the present invention and a control compound. In one embodiment the test compound is a phosphonic acid compound of the present invention and in another

embodiment the test compound is a prodrug thereof. In one embodiment the control compound is a phosphorus-containing compound of the present invention. In another embodiment the control compound is the corresponding carboxylic acid derivative of the phosphorus-containing test compound.

[0134] The term "enhanced oral bioavailability" refers to an increase of at least 50% of the absorption of the dose of the parent drug, unless otherwise specified. In an additional aspect the increase in oral bioavailability of the prodrug (compared to the parent drug) is at least 100%, that is a doubling of the absorption. Measurement of oral bioavailability usually refers to measurements of the prodrug, drug, or drug metabolite in blood, plasma, tissues, or urine following oral administration compared to measurements following systemic administration of the compound administered orally.

[0135] The terms "treating" or "treatment" of a disease includes a slowing of the progress or development of a disease after onset or actually reversing some or all of the disease affects. Treatment also includes palliative treatment.

[0136] The term "preventing" includes a slowing of the progress or development of a disease before onset or precluding onset of a disease.

[0137] The term "thyroid hormone receptors" (TR) refers to intracellular proteins located in cell nuclei that, following the binding of thyroid hormone, stimulate transcription of specific genes by binding to DNA sequences called thyroid hormone response elements (TREs). In this manner TR regulates the expression of a wide variety of genes involved in metabolic processes (*e.g.*, cholesterol homeostasis and fatty acid oxidation) and growth and development in many tissues, including liver, muscle and heart. There are at least two forms of TR; TR alpha (on chromosome 17) and TR beta (on chromosome 3). Each of these isoforms also has two main isoforms: TR alpha-1 and TR alpha-2; and TR beta-1 and TR beta-2, respectively. TRs are high affinity receptors for thyroid hormones, especially triiodothyronine.

[0138] The term "ACC" refers to acetyl CoA carboxylase.

[0139] The term "FAS" refers to fatty acid synthase.

[0140] The term "spot-14" refers to a 17 kilodalton protein expressed in lipogenic tissues and is postulated to play a role in thyroid hormone

stimulation of lipogenesis. (Campbell, MC *et al., Endocrinology 10*:1210 (2003).

[0141] The term "CPT-1" refers to carnitine palmitoyltransferase-1.

[0142] The term "CYP7A" refers to cholesterol 7-alpha hydroxylase, which is a membrane-bound cytochrome P450 enzyme that catalyzes the 7-alpha-hydroxylation of cholesterol in the presence of molecular oxygen and NADPH-ferrihemoprotein reductase. This enzyme, encoded by CYP7, converts cholesterol to 7-alpha-hydroxycholesterol which is the first and rate-limiting step in the synthesis of bile acids.

[0143] The term "apoAI" refers to Apolipoprotein AI found in HDL and chylomicrons. It is an activator of LCAT and a ligand for the HDL receptor.

[0144] The term "mGPDH" refers to mitochondrial glycerol-3-phosphate dehydrogenase.

[0145] The term "hypercholesterolemia" refers to presence of an abnormally large amount of cholesterol in the cells and plasma of the circulating blood.

[0146] The term "hyperlipidemia" or "lipemia" refers to the presence of an abnormally large amount of lipids in the circulating blood.

[0147] The term "atherosclerosis" refers to a condition characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries wherein such deposits provoke fibrosis and calcification. Atherosclerosis raises the risk of angina, stroke, heart attack, or other cardiac or cardiovascular conditions.

[0148] The term "obesity" refers to the condition of being obese. Being obese is defined as a body mass index (BMI) of 30.0 or greater; and extreme obesity is defined at a BMI of 40 or greater. "Overweight" is defined as a body mass index of 25.0 to 29.9 (This is generally about 10 percent over an ideal body weight)

[0149] The term "coronary heart disease" or "coronary disease" refers to an imbalance between myocardial functional requirements and the capacity of the coronary vessels to supply sufficient blood flow. It is a form of myocardial ischemia (insufficient blood supply to the heart muscle) caused by a decreased capacity of the coronary vessels.

[0150] The terms "fatty liver" and "liver steatosis" are interchangeable and refer to a disease or disorder characterized by significant lipid deposition in the liver hepatocytes (parenchyma cells). Simple fatty liver or liver steatosis is not associated with any other liver abnormalities such as scarring or inflammation. Fatty liver or liver steatosis is a common in patients who are very overweight or have diabetes mellitus.

[0151] The term "NonAlcoholic SteatoHepatitis (NASH) refers to a disease or disorder characterized by inflammation of the liver in combination with fatty liver. NASH is a possible diagnosis when other causes of liver inflammation such as hepatitis B and C viruses, autoimmune disorders, alcohol, drug toxicity, and the accumulation of copper (Wilson's Disease) or iron (hemochromatosis) are excluded.

[0152] The term "NonAlcoholic Fatty Liver Disease (NAFLD) refers to a wide spectrum of liver disease ranging from (and including) simple fatty liver (steatosis) to nonalcoholic steatohepatitis (NASH), to cirrhosis (advanced scarring of the liver). All of the stages of NAFLD have fatty liver in common. In NASH, fat accumulation is associated with varying degrees of inflammation (hepatitis) which may lead to scarring (fibrosis) of the liver.

[0153] Steatosis can be most readily diagnosed with noninvasive imaging modalities, such as ultrasound, magnetic resonance imaging, or computed tomography as examples, or following a percutaneous biopsy. Using ultrasound as an example of a noninvasive imaging diagnosis tool: the sonographic findings of diffuse fatty change include a diffuse hyperechoic echotexture (bright liver), increased liver echotexture compared with the kidneys, vascular blurring, and deep attenuation (Yajima *et al., Tohoku J Exp Med 139(1):*43–50 (1983)). Using percutaneous biopsy, the histological features of NAFLD are indistinguishable from those of alcohol-induced liver disease, of which, predominant macrovesicular steatosis alone in >33% of hepatocytes will be used as the definition. Other histologic features, such as varying amounts of cytologic ballooning and spotty necrosis, scattered mixed neutrophilic-lymphocytic inflammation, glycogen nuclei, Mallory's hyaline,

and perisinusoidal fibrosis may be present, but are not required for a diagnosis of NAFLD.

[0154] The term "nephrotic syndrome" refers to a condition of heavy glomerular proteinuria which is associated with hyperlipidemia, increased risk of cardiovascular disease, and deterioration or renal function. The nephrotic dyslipidemia is marked by hypercholesterolemia, hypertriglyceridemia, elevated plasma concentration and impaired clearance of LDL, VLDL, and IDL. These abnormalities are largely a result of dysregulation of the key enzymes and receptors involved in lipid metabolism, including LDL receptor deficiency, lecithin-cholesterol acyl transferase (LCAT) deficiency, elevated plasma cholesterol ester transfer protein, diminished HDL receptor, dysregulation of HMG-CoA reductase and 7α-hydroxylase, diminished catabolism of apo B-100, increased production of Lp(a), downregulation of lipoprotein lipase VLDL receptor and hepatic lipase, and upregulation of hepatic acyl-coenzyme A:diacylglycerol acyltransferase, acetyl-coenzyme A carboxylase, and fatty acid synthase.

[0155] The term "chronic renal failure" refers to a chronic kidney condition that leads to abnormalities of lipid metabolism and marked alteration of plasma lipid profile. The typical dyslipidemia associated with chronic renal failure includes hypertriglyceridemia, elevated level and impaired clearance of VLDL, IDL, and LDL, inappropriately reduced HDL cholesterol, and impaired maturation of cholesterol-poor HDL-3 to cardioprotective cholesterol ester-rich HDL-2.The primary mechanisms for the dyslipidemia include downregulation of lipoprotein lipase, VLDL receptor, hepatic triglyceride lipase, and LCAT.

[0156] The term "diabetes" refers to a heterogeneous group of disorders that share glucose intolerance in common. It refers to disorders in which carbohydrate utilization is reduced and that of lipid and protein enhanced; and may be characterized by hyperglycemia, glycosuria, ketoacidosis, neuropathy, or nephropathy.

[0157] The term "non-insulin-dependent diabetes mellitus" (NIDDM or type 2 diabetes) refers to a heterogeneous disorder characterized by impaired insulin

secretion by the pancreas and insulin resistance in tissues such as the liver, muscle and adipose tissue. The manifestations of the disease include one or more of the following: impaired glucose tolerance, fasting hyperglycemia, glycosuria, increased hepatic glucose output, reduced hepatic glucose uptake and glycogen storage, reduced whole body glucose uptake and utilization, dyslipidemia, fatty liver, ketoacidosis, microvascular diseases such as retinopathy, nephropathy and neuropathy, and macrovascular diseases such as coronary heart disease.

[0158] The term "impaired glucose tolerance (IGT)" refers to a condition known to precede the development of overt type 2 diabetes. It is characterized by abnormal blood glucose excursions following a meal. The current criteria for the diagnosis of IGT are based on 2-h plasma glucose levels post a 75g oral glucose test (144-199 mg/dL). Although variable from population to population studied, IGT progresses to full blown NIDDM at a rate of 1.5 to 7.3% per year, with a mean of 3-4% per year. Individuals with IGT are believed to have a 6 to 10-fold increased risk in developing NIDDM. IGT is an independent risk factor for the development of cardiovascular disease.

[0159] The term "insulin resistance" is defined clinically as the impaired ability of a known quantity of exogenous or endogenous insulin to increase whole body glucose uptake and utilization. As insulin regulates a wide variety of metabolic processes in addition to glucose homeostasis (*e.g.*, lipid and protein metabolism), the manifestations of insulin resistance are diverse and include one or more of the following: glucose intolerance, hyperinsulinemia, a characteristic dyslipidemia (high triglycerides; low high-density lipoprotein cholesterol, and small, dense low-density lipoprotein cholesterol), obesity, upper-body fat distribution, fat accumulation in the liver (non-alcoholic fatty liver disease), NASH (non-alcoholic steatohepatitis), increased hepatic glucose output, reduced hepatic glucose uptake and storage into glycogen, hypertension, and increased prothrombotic and antifibrinolytic factors. This cluster of cardiovascular-metabolic abnormalities is commonly referred to as "The Insulin Resistance Syndrome" or "The Metabolic Syndrome" and may

lead to the development of type 2 diabetes, accelerated atherosclerosis, hypertension or polycystic ovarian syndrome.

[0160] The Metabolic Syndrome" or "Metabolic Syndrome X" is characterized by a group of metabolic risk factors in one person. They include:

- Central obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia (blood fat disorders — mainly high triglycerides and low HDL cholesterol — that foster plaque buildups in artery walls)
- Raised blood pressure (130/85 mmHg or higher)
- Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor [–1] in the blood)
- Proinflammatory state (*e.g.*, elevated high-sensitivity C-reactive protein in the blood)

[0161] According to the present invention, "Metabolic Syndrome" or "Metabolic Syndrome X" is identified by the presence of three or more of these components:

- Central obesity as measured by waist circumference:
  Men: Greater than 40 inches
  Women: Greater than 35 inches
- Fasting blood triglycerides greater than or equal to 150 mg/dL
- Blood HDL cholesterol:
- Men: Less than 40 mg/dL
- Women: Less than 50 mg/dL
- Blood pressure greater than or equal to 130/85 mmHg
- Fasting glucose greater than or equal to 110 mg/dL

[0162] The term "thyroid responsive element" or "TRE" refers to an element that usually consists of directly repeated half-sites with the consensus sequence AGGTCA. (Harbers *et al., Nucleic Acids Res. 24(12)*:2252–2259

(1996)). TREs contain two half-sites of the AGGTCA motif which can be arranged as direct repeats, inverted repeats, or everted repeats.

[0163] The term "thyroid responsive genes" refers to genes whose expression is affected by triiodothyronine (Menjo *et al., Thyroid 9(9)*:959-67 (1999); Helbing *et al., Mol. Endocrinol. 17(7)*:1395-409 (2003)).

[0164] The term "TSH" or "thyrotropin" refers to the thyroid stimulating hormone.

[0165] The term "atherogenic proteins" refers to proteins that induce, stimulate, enhance or prolong atherosclerosis and diseases related to atherosclerosis, including but not limited to coronary heart disease. Atherogenic proteins include apoAI and Lp (a).

[0166] The term "thyroid hormone, or TH" includes for example natural iodinated thyronines from thyroglobulin (*e.g.*, T3, T4), as well as drugs such as Levothyroxine sodium which is the sodium salt of a levorotatory isomer of T4 and a commonly used drug as replacement therapy in hypothyroidism. Other uses include the treatment of simple nonendemic goiter, chronic lymphocytic thyroiditis and thyrotropin-dependent thyroid carcinoma. Liothyronine sodium is the sodium salt of a levorotatory isomer of T3. Liotrix is a 4:1 mixture of levothyroxine and liothronine. Thyroid is a preparation derived from dried and defatted thyroid glands of animals.

[0167] The term "thyromimetic" or "T3 mimetic" as used herein, is intended to cover any moiety which binds to a thyroid receptor and acts as an agonist, antagonist or partial agonist/antagonist of T3. The thyromimetic may be further specified as an agonist, an antagonist, a partial agonist, or a partial antagonist. The thyromimetics of the present invention presumably bind the T3 binding site and can inhibit T3 binding to a thyroid hormone receptor utilizing a heterologous displacement reaction. Thyromimetics of the present invention that can produce one of or more of the effects mediated by naturally occurring L-triiodothyronine in a target tissue or cell would be considered an agonist or partial agonist. Thyromimetics of the present invention that can inhibit one of more of the effects mediated by naturally occurring L-

triiodothyronine in a target tissue or cell would be considered an antagonist, partial agonist, or inverse agonist.

[0168] The term "metabolic disease" includes diseases and conditions such as obesity, diabetes and lipid disorders such as hypercholesterolemia, hyperlipidemia, hypertriglyceridemia as well as disorders that are associated with abnormal levels of lipoproteins, lipids, carbohydrates and insulin such as metabolic syndrome X, diabetes, impaired glucose tolerance, atherosclerosis, coronary heart disease, cardiovascular disease.

[0169] The term "mitochondrial biogenesis" or "mitochondrialgenesis" refers to the rate at which nascent mitochondria are synthesized. Mitochondrial biogenesis that occurs during cell replication provides enough new mitochondria for both the parent and daughter cells. Mitochondrial biogenesis that occurs in the absence of cell replication leads to an increase in the number of mitochondria within a cell.

[0170] As used herein, the term "significant" or "statistically significant" means a result (*i.e.* experimental assay result) where the p-value is ≤ 0.05 (*i.e.* the chance of a type I error is less than 5%) as determined by an art-accepted measure of statistical significance appropriate to the experimental design.

[0171] All references cited herein are incorporated by reference in their entirety.

Detailed Description of the Invention

[0172] The present invention relates to methods of preventing or treating metabolic diseases with phosphinic acid-containing compounds, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs, where the phosphinic acid-containing compounds bind to a thyroid hormone receptor.

[0173] Thyroid hormones and thyroid hormone mimetics bind to thyroid hormone receptors in the nucleus of cells and can change expression levels of genes encoding proteins that play an important role in metabolic diseases. Metabolic diseases that can be prevented or treated with thyroid hormone

mimetics include obesity and lipid disorders such as hypercholesterolemia, hyperlipidemia, and hypertriglyceridemia as described in further detail below. Other metabolic diseases that can be prevented or treated with thyroid hormone mimetics include fatty liver/steatosis, NAFLD, NASH, diabetes, impaired glucose tolerance, and insulin resistance. Conditions associated with these diseases, such as atherosclerosis, coronary artery disease, and heart failure, can also be treated with these thyroid hormone receptor binding compounds.

[0174] Prior to the discoveries of the present invention, phosphinic acids were thought to be a poor replacement for carboxylic acids based on differences in geometry, size, and charge. Phosphinic acids can also show reduced binding affinities against enzymes that utilize or bind the analogous carboxylic acid. Phosphinic acids can also display differences in cellular and *in vivo* potency, oral bioavailability, pharmacokinetics, metabolism, and safety. T3 and previously reported T3 mimetics contain a carboxylic acid thought to be important for binding and activation of T3 responsive genes. The carboxylic acid may also be important in the transport and distribution of these compounds through various transport proteins. Transport proteins can enhance transport of certain compounds, particularly negatively charged compounds, to the nucleus.

[0175] Prior to the discoveries of the present invention it was therefore unclear whether replacement of a carboxylic acid with a phosphinic acid would produce a compound that is efficacious as a T3 mimetic because of the following:

1. it was not known whether a T3 mimetic with a phosphinic acid in place of the carboxylic acid would be transported into liver cell across the cellular membrane;

2. if the phosphinic acid-containing T3 mimetic were transported across the cellular membrane of liver cells, it was not known whether the compound would be transported across the nuclear membrane into the nucleus;

3. if the phosphinic acid-containing T3 mimetic were transported across both the cellular membrane and the nuclear membrane of the liver cell, it was not known if the compound would bind to the TR receptor with a great enough affinity to be efficacious;

4. if the phosphinic acid-containing T3 mimetic were transported across both the cellular membrane and the nuclear membrane of the liver cell, and bound to the TR receptor with sufficient affinity for receptor activity, it was not known whether the compound would act as an agonist or antagonist of receptor activity;

5. if the phosphinic acid-containing T3 mimetic were transported across both the cellular membrane and the nuclear membrane of the liver cell, and bound to the TR receptor with sufficient affinity for receptor activation, and acted as an agonist of receptor activity, it was unknown whether the compound would have a high enough tissue selectivity and have a therapeutic index great enough to be efficacious in treating the diseases and disorders described herein while avoiding undesired side-effects involving the heart.

6. finally, even if the if the phosphinic acid-containing T3 mimetic were transported across both the cellular membrane and the nuclear membrane of the liver cell, and bound to the TR receptor with sufficient affinity for receptor activation, and acted as an agonist of receptor activity, and had a high enough tissue selectivity and had a therapeutic index great enough to be efficacious in treating the diseases and disorders described herein while avoiding undesired side-effects involving the heart, it was not known if the compounds of the present invention would be rapidly cleared from the blood by the kidneys thereby making the compound less useful as a drug compound.

[0176] Thus, it was unexpected when the present Inventors discovered that the phosphinic acid T3 mimetic compounds of the present invention are capable of being effectively transported across the cellular membrane into liver cells and across the nuclear membrane where they bind the thyroid receptors and

activate thyroid hormone responsive genes. Further, surprisingly the present Inventors discovered that the compounds of the present invention bind to the thyroid receptors with sufficient binding affinity to be effective in activating the receptors. Still further surprisingly, the present Inventors discovered that the compounds of the present invention act as agonists rather than antagonists and are thus effective in activating thyroid hormone responsive genes and for the uses described herein, such as lowering cholesterol. Still further surprisingly, the present Inventors discovered that the compounds of the present invention are effective in activating thyroid hormone responsive genes and for the uses described herein, such as lowering cholesterol, even for compounds of the present invention that bind to the thyroid hormone receptors with reduced affinity as compared to the corresponding carboxylic acid derivative. Still further surprisingly, the present Inventors discovered that the compounds of the present invention have a high enough tissue selectivity and have a therapeutic index great enough to be efficacious in treating the diseases and disorders described herein while avoiding undesired side-effects involving the heart.

[0177] It is well known that many phosphinic acids in the blood are quickly cleared by the kidneys thereby greatly diminishing their usefulness as drugs in many cases. When the Inventors of the present invention discovered that prodrugs of the compounds of the present invention were excreted into the blood stream as active phosphinic acids after being processed in the liver, it was not known whether the active compound would be quickly cleared by the kidneys or whether the phosphinic acid would be re-absorbed or transported into the liver. It was therefore unexpected when the present Inventors discovered that the active phosphinic acid compounds of the present invention were not rapidly cleared by the kidneys. It was also unexpected when the present Inventors discovered that the active phosphinic acid compounds of the present invention were re-absorbed or transported back into the liver. In fact, it was surprisingly found that the liver was the main mode of clearance of compounds tested.

[0178] In one aspect, the phosphinic acid-containing compounds, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs used in these methods bind to at least one thyroid hormone receptor with an Ki of ≤ 100 nM relative to T3, or ≤ 90nM, ≤ 80nM, ≤ 70nM, ≤ 60nM, ≤ 50nM, ≤ 40nM, ≤ 30nM, ≤ 20nM, ≤ 10nM, ≤ 50nM, ≤ 1nM, ≤ 0.5nM. Thyroid hormone receptor binding is readily determined using assays described in the literature. For example, nuclear extracts from animal livers can be prepared according to the methods described by Yokoyama *et al.* (*J. Med. Chem. 38*:695-707 (1995)). Binding assays can also be performed using purified thyroid hormone receptors. For example, using the methods used by Chiellini *et al.* (*Bioorg. Med. Chem.* 10:333-346 (2002)), competition ligand binding affinities are determined using ^{125}I-T3 and the human thyroid receptors TRα1 and TRβ1. The latter methods advantageously enable determination of thyroid receptor selectivity. Methods described in Example A were used to determine the binding of compounds of this invention.

[0179] In another aspect, the phosphinic acid-containing compounds, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs used in these methods cause at least a 50%, 2 fold, 3 fold, 4 fold, 6 fold or 8 fold increase or decrease in the expression of one or more thyroid hormone-responsive genes. Changes in gene expression can be detected in cells or *in vivo*. Prodrugs of the phosphinic acid-containing compounds can increase cellular uptake but in some cases are poorly converted to the phosphonic acid or monoester due to low levels of the enzymes required for the conversion. Changes in gene expression *in vivo* require either the phosphinic acid of the invention to be taken up by the tissue following administration or for the prodrug remain intact after administration long enough to distribute to the target organ and cell. Following distribution to the cell, enzymes responsible for cleaving the prodrug must act on the prodrug and convert it to the phosphinic acid. The compound must then be able to be transported to the nucleus. If a portion of the compound is excreted from the cell it must be retransported back across the cellular membrane and

nuclear membrane. The prodrugs of the present invention that are activated in the liver and excreted by the liver as phosphinic acid compounds are retransported back across the cellular and nuclear membrane and into the nucleus. Despite being excreted from the liver and having to be retransported into the nucleus and despite having reduced potency *in vivo*, the phosphinic acid-containing compounds and their prodrugs led to surprisingly potent biological activity. This surprisingly high biological activity is attributed to the ability of the compounds of the present invention to modulate genes known to be regulated by T3. For example, mGPDH increased > 1.5-fold in the liver of an animal administered a 1 mg/kg dose of the drug.

[0180] The liver is a major target organ of thyroid hormone with an estimated 8% of the hepatic genes regulated by thyroid hormone. Quantitative fluorescent-labeled cDNA microarray hybridization was used to identify thyroid-responsive genes in the liver as shown in Table 1 below (Feng *et al., Mol. Endocrinol. 14*:947-955 (2000)). Hepatic RNA from T3-treated and hypothyroid mice were used in the study. Thyroid hormone treatment affected the expression of 55 genes from the 2225 different mouse genes sampled with 14 increasing >2-fold and 41 decreasing >60%.

List of Hepatic Genes Regulated by T3 Determined by cDNA Microarray Analyses			
Function Clone ID	Genes	Accession No.	Fold
Carbohydrate and fatty acid metabolism, and insulin action			
580906	*Spot 14 gene*	*X95279*	*8.8*
523120	*Glucose-6-phosphatase*	*U00445*	*3.8*
615159	*Carbonyl reductase (Cbr1)*	*U31966*	*3.3*
571409	*Insulin-like growth factor binding protein 1 precursor*	*X81579*	*3.0*
481636	*Fatty acid transport protein (FATP)*	*U15976*	*1.8*
550993	Cyp4a-10	X69296	0.3
583329	PHAS-II	U75530	0.3
616283	Serine/threonine kinase (Akt2)	U22445	0.3
583333	Putative transcription factor of the insulin gene	X17500	0.3
533177	Nuclear-encoded mitochondrial acyltransferase	L42996	0.2
608607	Glycerophosphate dehydrogenase	J02655	0.3
Cell proliferation, Replication			
614275	*B61*	*U26188*	*2.3*
597868	*Bcl-3*	*M90397*	*2.5*
493127	*Kinesin-like protein (Kip1p)*	*AF131865*	*2.0*

List of Hepatic Genes Regulated by T3 Determined by cDNA Microarray Analyses			
Function Clone ID	Genes	Accession No.	Fold
582689	Chromodomain-helicase-DNA binding protein CHD-1	P40201	0.4
524471	NfiB1-protein (exon 1–12)	Y07685	0.3
516208	Putative ATP-dependent RNA helicase PL10	J04847	0.3
558121	Murine vik5variant in the kinase	S53216	0.1
573247	C11 protein	X81624	0.3
522108	Thymic stromal stimulating factor	D43804	0.3
613942	Ubiquitin-activating enzyme E1 X	D10576	0.3
Signal transduction			
573046	*β-2 Adrenergic receptor*	*X15643*	*3.4*
583258	*Protein kinase C inhibitor (mPKCI)*	*U60001*	*2.1*
616040	Inhibitory G protein of adenylate cyclase, α chain	M13963	0.3
583353	Terminal deoxynucleotidyltransferase	04123	0.3
550956	Rho-associated, coiled-coil forming protein kinase p160	U58513	0.2
582973	Protein kinase C, Θ type	AB011812	0.3
442989	Protein kinase ζ	M94632	0.5
607870	Lamin A	D13181	0.3
Glycoprotein synthesis			
375144	α-2,3-Sialyltransferase	D28941	0.3
481883	β-Galactoside α 2,6-sialyltransferase	D16106	0.3
Cellular immunity			
615872	T-complex protein 1, d subunit	P80315	0.3
618426	H-2 class I histocompatibility antigen	Q61147	0.3
614012	FK506-binding protein (FKBP65)	L07063	0.3
604923	FK506-binding protein (FKBP23)	AF040252	0.2
Cytoskeletal protein			
374030	*Myosin binding protein H (MyBP-H)*	*U68267*	*2.2*
613905	AM2 receptor	X67469	0.3
616518	Cytoskeletal β-actin	X03672	0.3
614948	Actin, α cardiac	M15501	0.3
607364	Skeletal muscle actin	M12866	0.3
597566	Capping protein a-subunit	G565961	0.3
483226	Actin, γ-enteric smooth muscle	M26689	0.3
Others			
552837	Major urinary protein 2 precursor	M27608	3.9
521118	*β-Globin*	*AB020013*	*2.3*
493218	*α-Globin*	*L75940*	*2.7*
585883	Putative SH3-containing protein SH3P12	AF078667	0.3
615239	Membrane-type matrix metalloproteinase	X83536	0.2
402408	ece1 (endothelin-converting enzyme)	W78610	0.2
635768	α-Adaptin	P17426	0.3
634827	Glucose regulated protein 78	D78645	0.3
616189	Lupus la protein homolog	L00993	0.3
588337	EST	AI646753	0.4
335579	Virus-like (VL30) retrotransposon BVL-1	X17124	0.3

List of Hepatic Genes Regulated by T3 Determined by cDNA Microarray Analyses			
Function Clone ID	Genes	Accession No.	Fold
557037	TGN38B	D50032	0.3
597390	Mitochondrial genome	L07096	0.4
616563	Arylsulfatase A	X73230	0.3

[0181] Genes reported to be affected by thyroid hormone are identified using a variety of techniques include microarray analysis. Studies have identified genes that are affected by T3 and T3 mimetics that are important in metabolic diseases.

[0182] T3-responsive genes in the liver include genes affecting lipogenesis, including spot 14, fatty acid transport protein, malic enzyme, fatty acid synthase (Blennemann *et al., Mol. Cell. Endocrinol. 110(1-2)*:1-8 (1995)) and CYP4A. HMG CoA reductase and LDL receptor genes have been identified as affecting cholesterol synthesis and as being responsive to T3. CPT-1 is a T3-responsive gene involved in fatty acid oxidation. Genes affecting energy expenditure, including mitochondrial genes such as mitochondrial *sn*-glycerol 3-phosphate dehydrogenase (mGPDH), and/or enzymes associated with proton leakage such as the adenine nucleotide transporter (ANT), Na^+/K^+-ATPase, Ca^{2+}-ATPase and ATP synthase are also T3-responsive genes. T3-responsive genes affecting glycogenolysis and gluconeogenesis include glucose 6-phosphatase and PEPCK.

[0183] Thyroid hormone-responsive genes in the heart are not as well described as the liver but could be determined using similar techniques as described by Feng *et al.* Many of the genes described to be affected in the heart are the same as described above for the liver. Common genes evaluated include mitochondrial *sn*-glycerol 3-phosphate dehydrogenase (mGPDH), and myosin heavy and light chains (Danzi *et al., Thyroid 12(6)*:467-72 (2002)).

[0184] Compounds used in the methods bind to thyroid receptors and produce a change in some hepatic gene expression. Evidence for agonist activity is obtained using standard assays described in the literature. One assay commonly used entails a reporter cell assay wherein cells, *e.g.*, HeLa cells, Hek293 cells, or Chinese hamster ovary cells, are transfected with an expression vector for human TRα1 or TRβ1 and subsequently with a reporter

vector encoding a secreted form of alkaline phosphatase whose expression is under the control of a thyroid hormone response element. Agonist activity is measured by exposing the cells to the compounds, especially phosphorus-containing prodrugs of the compounds that are cleaved to the phosphonic acid, phosphinic acid, or monoester by cell homogenates, followed by determining alkaline phosphatase activity in the cell culture medium using a chemiluminescent assay (Grover *et al., Proc. Natl. Acad. Sci. U.S.A. 100(17)*:10067-72 (2003)).

[0185] In one aspect, the phosphinic acid-containing thyromimetics and their prodrugs and salts are useful in preventing or treating arteriosclerosis by modulating levels of atherogenic proteins, *e.g.*, Lp(a), apoAI, apoAII, LDL, HDL. Clinically overt hypothyroidism is associated with accelerated and premature coronary atherosclerosis and subclinical hypothyroidism is considered a condition with an increased risk for these diseases (Vanhaelst *et al.* and Bastenie *et al., Lancet* 2 (1967)).

[0186] T3 and T3 mimetics modulate atherogenic proteins in a manner that could prove beneficial for patients at risk to develop atherosclerosis or patients with atherosclerosis or diseases associated with atherosclerosis. T3 and T3 mimetics are known to decrease Lp(a) levels, *e.g.*, in the monkey, with 3,5-dichloro-4-[4-hydroxy-3-(1-methylethyl)phenoxy]benzeneacetic acid (Grover *et al., Proc. Natl. Acad. Sci. U.S.A. 100*:10067-10072 (2003)). In human hepatoma cells, the T3 mimetic CGS23425 ([[4-[4-hydroxy-3-(1-methylethyl)phenoxy]-3,5-dimethylphenyl]amino]oxo acetic acid) increased apoAI expression via thyroid hormone receptor activation (Taylor *et al., Mol. Pharm. 52*:542-547 (1997)).

[0187] Thus in one aspect, the phosphinic acid-containing thyromimetics, their salts and prodrugs can be used to treat or prevent atherosclerosis, coronary heart disease and heart failure because such compounds are expected to distribute to the liver (Examples F and H) and modulate the expression and production of atherogenic proteins.

[0188] In another aspect, the phosphinic acid-containing thyromimetics and their prodrugs and salts are useful for preventing and/or treating metabolic

diseases such as obesity, hypercholesterolemia and hyperlipidemia and conditions such as atherosclerosis, coronary heart disease, heart failure, nephrotic syndrome, and chronic renal failure without affecting thyroid function, thyroid production of circulating iodinated thyronines such as T3 and T4, and/or the ratio of T3 to T4. Compounds previously reported that contain a carboxylic acid moiety, *e.g.*, GC-1 ([4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy] acetic acid)(Trost *et al.*, *Endocrinology 141*:3057-3064 (2000)) and 3,5-Dichloro-4-[4-hydroxy-3-(1-methylethyl)phenoxy] benzeneacetic acid (Grover *et al.*, *Proc. Natl. Acad. Sci.* U.S.A. *100*:10067-10072 (2003)) report that these TRβ-selective compounds dose-dependently lower cholesterol and TSH levels. Effects on cholesterol and TSH occur at the same dose or at doses stated to be not pharmacologically different (*e.g.*, 2-fold).

[0189] Particularly useful T3 mimetics in these methods would minimize effects on thyroid function, thyroid production of circulating iodinated thyronines such as T3 and T4, and/or the ratio of T3 to T4. Unlike prior T3 mimetics, the compounds or the present invention distribute more readily to the liver and result in pharmacological effects at doses that do not adversely affect thyroid function, thyroid production of circulating iodinated thyronines such as T3 and T4, and/or the ratio of T3 to T4. In one embodiment the compounds of the present invention have a therapeutic index, defined as the difference between the dose at which a significant effect is observed for a use disclosed herein, *e.g.*, lowering cholesterol, and the dose at which a significant decrease in T3 or significant decrease in T4, or significant change in the ratio of T3 to T4 is observed, is at least 50 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, 1000 fold, 2000 fold, 3000 fold, 4000 fold, 5000 fold, 6000 fold, 7000 fold, 8000 fold, 9000 fold or at least 10000 fold. In one embodiment, rather than a significant amount, the amount of change in T3 or T4 is a decrease selected from at least 5%, 10%, 15%, 20%, 25% or at least 30% of circulating levels.

[0190] In one embodiment, the phosphinic acid-containing thyromimetics and their prodrugs and salts are useful for significantly lowering cholesterol levels

without having a significant effect on TSH levels. In another embodiment, the compounds of the present invention significantly lower cholesterol levels without lowering TSH levels by more than 30%, 25%, 20%, 15%, 10%, or 5%.

[0191] Side effects associated with TH-based therapies limit their use for treating obese patients and according to the Physician's Desk Reference (PDR) T3 is now contraindicated for patients with obesity. 3,5-dichloro-4-[4-hydroxy-3-(1-methylethyl)phenoxy] benzeneacetic acid and other T3 mimetics are reported to result in weight loss in animals, *e.g.*, rodent models and monkeys. Weight loss from these compounds may arise from their effects on the liver as well as peripheral tissues. TH is known to have a multitude of effects outside of the liver that could result in increased metabolism and weight loss. TH plays an important role in the development and function of brown and white adipose tissue. TH can induce WAT differentiation, proliferation and intracellular lipid accumulation. TH induces lipogenic genes in WAT such as glucose-6-phosphate dehydrogenase, fatty acid synthase and spot-14. TH also regulates lipolysis in fat to produce weight loss in a coordinated manner, *i.e.*, lipolysis in fat to free fatty acids followed by free fatty acid utilization in tissues, *e.g.*, liver, muscle and heart.

[0192] Weight loss through administration of liver-specific T3 analogues requires that the increased oxygen consumption in the liver resulting from T3 is sufficient to result in net whole body energy expenditure. The liver's contribution to energy expenditure is estimated to be 22% based on oxygen consumption measurements. (Hsu, A *et al. Am. J. Clin. Nutr. 77(6)*:1506-11(2003)). Thus, the compounds of the present invention may be used to maintain or reduce weight in an animal.

[0193] Mitochondria are the fuel source for all cellular respiration. The synthesis of new mitochondria is a complex process which requires over 1000 genes (Goffart *et al., Exp. Physiol. 88(1)*:33-40 (2003)). The mechanisms which control mitochondrial biogenesis are not well defined, but are known to include exercise (Jones *et al., Am. J. Physiol. Endocrinol. Metab. 284(1)*:E96-101 (2003)), overexpression of PGC-1 (Lehman *et al., J. Clin. Invest.*

106(7):847-56 (2000)) or AMP activated protein kinase (Bergeron *et al., Am. J. Physiol. Endocrinol. Metab. 281(6)*:E1340-6 (2001)). An increase in mitochondrial density leads to a greater rate of energy expenditure. Thyroid hormone has been shown to play a key role in mitochondrial biogenesis by increasing expression of nuclear respiratory factor-1 and PGC-1 (Weitzel *et al., Exp. Physiol. 88(1)*:121-8 (2003)).

[0194] Compounds which increase the expression of NRF-1 and/or PGC-1 could lead to an increase in mitochondrial density within a cell. Such an increase would cause the cell to have a higher rate of energy expenditure. Methods to analyze NRF-1 and PGC-1 include immunoblotting with specific antibodies, or analysis of mRNA levels. Compounds that caused increases in NRF-1 or PGC-1 would therefore lead to a greater energy expenditure. Even small increases in energy expenditure over long periods of time (weeks to years) could cause a decrease in weight under isocaloric circumstances. Further methods for assessing mitochondrial biogenesis include the analysis of mitochondrial proteins such as cytochrome c and cytochrome c oxidase, either by immunoblotting or analysis of mRNA levels. Mitochondrial density can also be measured by counting the number of mitochondria in electron micrographs.

[0195] In one aspect, phosphinic acid-containing thyromimetics and their prodrugs and salts may be used to cause weight loss or prevent weight gain without side effects. It may be advantageous to use compounds that result in high liver specificity (Examples F and G). In one aspect, compounds that result in increased levels of genes associated with oxygen consumption, *e.g.*, GPDH (Example B), are particularly useful in weight loss and controlling weight gain. In another aspect, compounds that show weight loss at doses that do not affect cardiac function, *e.g.*, heart rate, force of systolic contraction, duration of diastolic relaxation, vascular tone, or heart weight, may be particularly useful in weight loss and controlling weight gain. In a further aspect, compounds that cause weight loss without affecting thyroid function, thyroid production of circulating iodinated thyronines such as T3 and T4, and/or the ratio of T3 to T4 are particularly useful.

[0196] Besides their use in obesity and weight control, phosphinic acid-containing thyromimetics and their prodrugs and salts may be used to treat diabetes and related conditions like impaired glucose tolerance, insulin resistance and hyperinsulinemia.

[0197] Patients with type 2 diabetes "T2DMs" exhibit chronic high blood glucose levels. High fasting blood glucose in T2DMs is related to the overproduction of glucose by a pathway in the liver known as the gluconeogenesis pathway. Throughput in this pathway is controlled in part by enzymes in the pathway such as PEPCK, fructose 1,6-bisphosphatase and glucose 6-phosphatase as well as by hormones such as insulin, which can influence the expression and activities of these enzymes. T3 is known to worsen diabetes. While the reason T3 worsens diabetes is not known, T3's effect on increasing the gene expression of PEPCK and glucose-6-phosphatase may be the cause of increased glucose levels. T3 is known to increase lipolysis of triglyceride pools in fat and to increase circulating levels of free fatty acids. (K.S. Park, *et al., Metabolism 48(10)*:1318-21 (1999)) T3's effect on free fatty acid levels may also be responsible for the negative effect on diabetes because high free fatty acid levels enhance flux through the gluconeogenesis pathway.

[0198] Compounds of this invention, while they mimic T3, result in preferential activation of liver T3 genes, are not expected to increase lipolysis in peripheral tissues which is expected to avoid the T3-induced higher circulating levels of free fatty acids and their effects on increasing gluconeogenesis flux and decreasing insulin sensitivity. Increased hepatic insulin sensitivity will decrease PEPCK and glucose 6-phosphatase gene expression thus reducing gluconeogenesis. TR activation in the liver should also decrease liver fat content, which in turn is expected to improve diabetes and steatohepatitis (*e.g.*, NASH), thus providing another use for the compounds of the present invention. A decrease in liver fat content is associated with increased hepatic insulin sensitivity (Shulman, 2000) and accordingly should improve glycemic control in type 2 diabetics through decreased glucose production and enhanced glucose uptake. The overall

effect on the patient will be better glycemic control, thus providing another use for the compounds of the present invention.

[0199] TH also stimulates GLUT-4 transporter expression in skeletal muscle which produces concomitant increases in basal glucose uptake. Studies in obese, insulin-resistant Zucker rats showed that TH therapy induces GLUT-4 expression in skeletal muscle and total amelioration of the hyperinsulinemia, although plasma glucose levels were moderately elevated (Torrance *et al. Endocrinology 138*:1204 (1997)). Thus another embodiment of the present invention relates to the use of compounds of the present invention to prevent or treat hyperinsulinemia.

[0200] TH therapy results in increased energy expenditure. Increased energy expenditure can result in increased weight loss, which in turn can result in improved glycemic control. Diet and exercise are often used initially to treat diabetics. Exercise and weight loss increase insulin sensitivity and improve glycemia. Thus, further uses of the compounds of the present invention include increasing energy expenditure, increasing insulin sensitivity and improving glycemia.

[0201] In one aspect, the phosphinic acid-containing compounds of the present invention are useful for increasing levels of genes associated with gluconeogenesis (Example B). In another aspect, the compounds of the present invention are useful for decreasing hepatic glycogen levels. Further, compounds of the present invention result in amelioration of hyperinsulinemia and/or decreased glucose levels in diabetic animal models at doses that do not affect cardiac function, *e.g.*, heart rate, force of systolic contraction, duration of diastolic relaxation, vascular tone, or heart weight. In a further aspect, compounds of the present invention result in amelioration of hyperinsulinemia and/or decreased glucose levels in diabetic animal models at doses that do not affect thyroid function, thyroid production of circulating iodinated thyronines such as T3 and T4, and/or the ratio of T3 to T4.

[0202] As discussed above, the previous use of T3 and T3 mimetics to treat metabolic diseases have been limited by the deleterious side-effects on the heart. Previous attempts to overcome this limitation have focused on

selectively targeting the liver over the heart using T3 mimetics that selectively bind TRβ over TRα. Because the heart expresses mainly TRα, previous investigators have attempted to increase the therapeutic index of T3 mimetics by increasing the selectively of the compounds for TRβ which is expressed in the liver. Previous attempts have not focused on T3 mimetics that selectively distribute to the liver over the heart or at least have not been successful. Thus, rather than selecting for a particular tissue or organ, previous work has been directed to discovering T3 mimetics that act selectively at the receptor level after the drug is non-selectively distributed to both heart and liver tissue. It was therefore unexpected when the present Inventors discovered that the phosphinic acid-compounds of the present invention selectively distributed to the liver over the heart. The selective distribution to the liver over the heart was also found with prodrugs, that although were processed in the liver, were excreted from the liver into the blood stream as active phosphinic acid compounds. Thus the compounds of the present invention are able to selectively target the liver and thereby increase the therapeutic index as compared to T3 and T3 mimetics containing a carboxylic acid. The compounds of the present invention can therefore be dosed at levels that are effective in treating metabolic and other disorders where the liver is the drug target without significantly negatively affecting heart function.

[0203] Because of the selectivity of the phosphinic acid-containing compounds of the present invention for the liver over the heart, it is not necessary for the compound to have greater selectivity for TRβ over TRα, although this may be desired. In fact, surprisingly some of the compounds of the present invention selectively bind TRα over TRβ and are highly effective for the uses disclosed herein without having the negative side-effects normally associated with TRα selective compounds. Thus, included as an embodiment of the present invention are compounds of Formula I, II, III, VIII, X, XVI, and XVII that selectively bind TRβ over TRα by at least 5 fold, 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, 300 fold, 400 fold or at least 500 fold, and compounds of Formula I, II, III,

VIII, X, XVI, and XVII that selectively bind TRα over TRβ by at least 5 fold, 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, 300 fold, 400 fold or at least 500 fold.

[0204] Changes in the therapeutic index are readily determined using assays and methods well described in the literature. Genes in extrahepatic tissues are monitored using methods well understood by those skilled in the art. Assays include using cDNA microarray analysis of tissues isolated from treated animals. The sensitivity of the heart to T3 makes analysis of T3-responsive genes in the heart as well as the functional consequences of these changes on cardiac properties one further strategy for evaluating the therapeutic index of the compounds of the present invention. Cardiac genes measured include mGPDH and myosin heavy and light chain. One method of measuring the effects of T3 mimetics on the heart is by the use of assays that measure T3 mediated myosin heavy chain gene transcription in the heart. Compounds of the present invention were tested using the methods described in Examples B, D, and I.

[0205] In one embodiment the compounds of the present invention have a therapeutic index, defined as the difference between the dose at which a significant effect is observed for a use disclosed herein, *e.g.*, lowering cholesterol, and the dose at which a significant effect on a property or function, as disclosed herein (*e.g.*, heart rate), is observed, is at least 50 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, 1000 fold, 2000 fold, 3000 fold, 4000 fold, 5000 fold, 6000 fold, 7000 fold, 8000 fold, 9000 fold or at least 10000 fold. Examples of said use disclosed herein includes but is not limited to reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of a disease or disorder selected from the group consisting of atherosclerosis, hypercholesterolemia, hyperlipidemia, obesity, NASH, NAFLD, nephrotic

syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, and osteoporosis. Examples wherein the property or function is a cardiac property/function include but are not limited to cardiac hypertrophy (heart weight to body weight ratio), heart rate, and various hemodynamic parameters, including systolic and diastolic arterial pressure, end systolic left ventricular pressure and maximal speeds of contraction and relaxation.

[0206] A variety of methods are described that provide a means for evaluating the functional consequences of T3-cardiac action, including measurement of cardiac hypertrophy (heart weight to body weight ratio), heart rate, and various hemodynamic parameters, including systolic and diastolic arterial pressure, end-systolic left ventricular pressure and maximal speeds of contraction and relaxation using methods described by Trost *et al.*, (*Endocrinology 141*:3057-64 (2000)). Compounds of the present invention were tested using the methods described in Examples B, D, and I.

[0207] Other methods are also available to assess the therapeutic index including effects on muscle wasting and bone density. Compounds of the present invention were tested using the methods described in Examples C and G.

[0208] The therapeutic index is determined by administering to animals a wide range of doses and determining the minimal dose capable of inducing a response in the liver relative to the dose capable of inducing a response in the heart.

[0209] Phosphinic acids are often poorly transported into cultured cells. Accordingly, cell reporter assays, while often useful for confirming agonist activity, may not provide a suitable indication of potency. Thus, evidence of agonist activity is often more readily obtained *in vivo* for compounds of the present invention. *In vivo* assays include but are not limited to treating animals with phosphinic acid-containing compounds of the invention or a

prodrug thereof and monitoring the expression of T3-responsive genes in the liver or the functional consequences of changes of T3-responsive genes.

[0210] In one aspect, compounds useful in the novel methods bind to thyroid receptors and produce changes in the expression of two or more hepatic genes. Animals used for testing compounds useful in the methods include normal rats and mice, animals made hypothyroid using methods well described in the literature, including thyroid hormone receptor knockout mice (*e.g.*, $TR\alpha^{-/-}$ such as those used in Grover *et al.*, 2003), or animals exhibiting high cholesterol (*e.g.*, high cholesterol fed rat or hamster), obesity and/or diabetes (*e.g.*, *fa/fa* rat, Zucker diabetic fatty rat, *ob/ob* mice, *db/db* mice, high fat fed rodent). (Liureau *et al.*, *Biochem. Pharmacol. 35(10)*:1691-6 (1986); Trost *et al.*, *Endocrinology 141(9)*:3057-64 (2000); and Grover *et al.*, 2003). The drug or prodrug is administered by a variety of routes including by bolus injection, oral, and continuous infusion (Examples B, D and I). Animals are treated for 1-28 days and the liver, heart and blood are isolated. Changes in gene transcription relative to vehicle treated animals and T3-treated animals are determined using northern blot analysis, RNAase protection or reverse-transcription and subsequent PCR. While methods are available for monitoring changes in thousands of hepatic genes, only a small number need to be monitored to demonstrate the biological effect of compounds in this invention. Typically, genes such as spot-14, FAS, mGPDH, CPT-1, and LDL receptor are monitored. Changes of >1.5 fold in two or more genes is considered proof that the compound modulates T3-responsive genes *in vivo*. Alternative methods for measuring changes in gene transcription include monitoring the activity or expression level of the protein encoded by the gene. For instance, in cases where the genes encode enzyme activities (*e.g.*, FAS, mGPDH), direct measurements of enzyme activity in appropriately extracted liver tissue can be made using standard enzymological techniques. In cases where the genes encode receptor functions (*e.g.*, the LDL receptor), ligand binding studies or antibody-based assays (*e.g.*, Western blots) can be performed to quantify the number of receptors expressed. Depending on the

gene, TR agonists will either increase or decrease enzyme activity or increase or decrease receptor binding or number.

[0211] The functional consequences of changing the expression levels of hepatic genes responsive to T3 is many-fold and readily demonstrated using assays well described in the literature. Administering phosphinic acid-containing compounds that bind to a TR to animals can result in changes in lipids, including hepatic and/or plasma cholesterol levels; changes in lipoprotein levels including LDL-cholesterol, lipoprotein a (Lp(a)); changes in hepatic glycogen levels; and changes in energy expenditure as measured by changes in oxygen consumption and in some cases animal weight. For example, the effect on cholesterol is determined using cholesterol fed animals such as normal rats and hamsters, or TR$\alpha^{-/-}$ knockout mice. Cholesterol is measured using standard tests. Compounds of the present invention were tested using the methods described in Example D and I. Hepatic glycogen levels are determined from livers isolated from treated animals. Compounds of the present invention were tested using the methods described in Examples D and E. Changes in energy expenditure are monitored by measuring changes in oxygen consumption (MVo_2). A variety of methods are well described in the literature and include measurement in the whole animal using Oxymax chambers (U.S. Patent No. 6,441,015). Livers from treated rats can also be evaluated (Fernandez *et al., Toxicol. Lett. 69(2)*:205-10 (1993)) as well as isolated mitochondria from liver (Carreras *et al., Am. J. Physiol. Heart Circ. Physiol. 281(6)*:H2282-8 (2001)). Hepatocytes from treated rats can also be evaluated (Ismail-Beigi F *et al., J Gen Physiol. 73(3)*:369-83 (1979)). Compounds of the present invention were tested using the methods described in Examples C and G.

[0212] Phosphinic acid-containing compounds that bind to a TR modulate expression of certain genes in the liver resulting in effects on lipids (*e.g.*, cholesterol), glucose, lipoproteins, and triglycerides. Such compounds can lower cholesterol levels which is useful in the treatment of patients with hypercholesterolemia. Such compounds can lower levels of lipoproteins such as Lp(a) or LDL and are useful in preventing or treating atherosclerosis and

heart disease in patients. Such compounds can raise levels of lipoproteins such as apoAI or HDL and are useful in preventing or treating atherosclerosis and heart disease in patients. Such compounds can cause a reduction in weight. Such compounds can lower glucose levels in patients with diabetes.

[0213] Another aspect is compounds that in the presence of liver cells or microsomes result in compounds of Formula I, II, III, VIII, X, XVI, and XVII wherein X is phosphinic acid.

[0214] Also provided are methods of reducing plasma lipid levels in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter, is enantiomerically enriched or diastereomerically enriched, or a stereoisomer covered later. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomerically enriched mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0215] Also provided are methods of reducing plasma lipid levels in an animal wherein the lipid is cholesterol, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer. In

one embodiment said methods of reducing cholesterol results in a lowering of total cholesterol. In one embodiment said methods of reducing cholesterol results in a reduction of high density lipoprotein (HDL). In one embodiment said methods of reducing cholesterol results in a reduction of low density lipoprotein (LDL). In one embodiment said methods of reducing cholesterol results in a reduction of very low density lipoprotein (VLDL). In another embodiment said LDL is reduced to a greater extent than said HDL. In another embodiment said VLDL is reduced to a greater extent than said HDL. In another embodiment said VLDL is reduced to a greater extent than said LDL.

[0216] In one embodiment of the method of reducing lipids, the lipid is triglycerides. In one embodiment said lipid is liver triglycerides. In another embodiment said lipid is in the form of a lipoprotein. In another embodiment said lipoprotein is Lp(a). In another embodiment said lipoprotein is apoAII.

[0217] Also provided are methods of increasing the ratio of HDL to LDL, HDL to VLDL, LDL to VLDL, apoAI to LDL or apoAI to VLDL in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII,, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII, or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0218] Also provided are methods of treating hyperlipidemia or hypercholesterolemia in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII., a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In

another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0219] Also provided are methods of preventing or treating atherosclerosis in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0220] Also provided are methods of reducing fat content in the liver or of preventing or treating fatty liver/steatosis, NASH or NAFLD in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0221] Also provided are methods of preventing or treating nephrotic syndrome or chronic renal failure in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0222] Also provided are methods of reducing weight or preventing weight gain in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0223] Also provided are methods of preventing or treating obesity in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter.

In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0224] Also provided are methods of preventing or treating coronary heart disease in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0225] Also provided are methods of maintaining or improving glycemic control in an animal being treated with a T3 mimetic, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer. In one embodiment said glycemic control is maintained after said animal is treated for at least 14 days with said

compound. In another embodiment said glycemic control is improved by 28 days in an animal treated with said compound.

[0226] Also provided are methods of lowering blood glucose levels in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0227] Also provided are methods of preventing or treating diabetes, insulin resistance, metabolic syndrome X or impaired glucose tolerance in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0228] Also provided are methods of preventing or treating altered energy expenditure in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another

embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0229] Also provided are methods of preventing or treating a liver disease responsive to modulation of T3-responsive genes in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0230] Also provided are methods of preventing or treating thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as

a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0231] Also provided are methods of increasing mitochondrial biogenesis in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0232] Also provided are methods of increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0233] Also provided are methods of inhibiting hepatic gluconeogenesis in an animal, the method comprising the step of administering to a patient an amount of a compound of Formula I, II, III, VIII, X, XVI, and XVII, a prodrug thereof, or a pharmaceutically acceptable salt or co-crystal thereof. In one embodiment said compound is an active form. In another embodiment said

compound is a prodrug. In another embodiment said compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof comprises a stereocenter. In another embodiment said compound is administered as a racemic mixture. In another embodiment said compound is administered as an enantiomerically enriched mixture. In another embodiment said compound is a administered as a diastereomeric mixture. In still another embodiment said compound is administered as an individual stereoisomer.

[0234] Also provided are kits for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis, or for the prevention or treatment of a disease or disorder for which a compound of the present invention is effective in preventing or treating, the kits comprising:

a) a pharmaceutical composition comprising a compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof; and

b) at least one container for containing said pharmaceutical composition.

[0235] Also provided are pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable excipient, carrier or diluent. Also provided are pharmaceutical compositions comprising a first pharmaceutical compound selected from Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof and a second pharmaceutical compound of the same Formula but wherein said first and second pharmaceutical compounds are not the same molecules. Also provided are pharmaceutical compositions comprising a first pharmaceutical compound selected from Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof and a second pharmaceutical compound selected from Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof, but wherein said first and said second pharmaceutical compounds are not both from the same Formula. Also provided are pharmaceutical compositions comprising a first pharmaceutical compound

selected from Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof and a second pharmaceutical compound that is not a compound selected from Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof.

[0236] Also provided are pharmaceutical compositions comprising a first compound of the present invention and a second compound useful for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of atherosclerosis, hyperlipidemia, hypercholesterolemia, obesity, fatty liver/steatosis, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis. In one embodiment, a composition comprising said first and second compound is a single unit dose. In another embodiment, said unit does is in the form of a tablet, hard capsule or soft gel capsule.

[0237] Also provided are pharmaceutical compositions of the present invention having an oral bioavailability of least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% 75% or at least 80%.

[0238] Also provided are kits for the prevention or treatment of a disease or disorder for which a compound of the present invention is effective in preventing or treating, the kits comprising:

a) a first pharmaceutical composition comprising a compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof;

b) a second pharmaceutical composition comprising an additional compound useful for the treatment or prevention of a disease or disorder for which a compound of the present invention is effective in preventing or treating; and

c) at least one container for containing said first or second or both first and second pharmaceutical composition.

[0239] Also provided are kits for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of a disease or disorder selected from the group consisting of atherosclerosis, hyperlipidemia, hypercholesterolemia, obesity, fatty liver/steatosis, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, and osteoporosis, the kits comprising:

a) a first pharmaceutical composition comprising a compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof;

b) a second pharmaceutical composition comprising an additional compound useful for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of atherosclerosis, hyperlipidemia, hypercholesterolemia, obesity, fatty liver/steatosis, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis; and

c) at least one container for containing said first or second or both first and second pharmaceutical composition.

[0240] Also provided are methods for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of atherosclerosis, hyperlipidemia, hypercholesterolemia, obesity, fatty liver/steatosis, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis the methods comprising the step of administering to a patient a therapeutically effective amount of 1) a first pharmaceutical composition comprising a compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof, and 2) a second pharmaceutical composition, wherein said second pharmaceutical composition is either another compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof, or is not another compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof.

[0241] Also provided are methods for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of atherosclerosis, hyperlipidemia, hypercholesterolemia, obesity, fatty liver/steatosis, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis the methods comprising the step of administering to a patient a therapeutically effective amount of 1) a first pharmaceutical composition comprising a compound of Formula I, II, III, VIII, X, XVI, and XVII or a prodrug thereof and 2) a second pharmaceutical

composition that is effective alone for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of atherosclerosis, hyperlipidemia, hypercholesterolemia, obesity, fatty liver/steatosis, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis.

[0242] Also provided is the use of a compound of the present invention for the manufacture of a medicament for reducing lipid levels, increasing the ratio of HDL to LDL or apoAI to LDL, reducing weight or preventing weight gain, maintaining or improving glycemic control, lowering blood glucose levels, increasing mitochondrial biogenesis, increasing expression of PGC-1, AMP activated protein kinase or nuclear respiratory factor, inhibiting hepatic gluconeogenesis or for the treatment or prevention of atherosclerosis, hypercholesterolemia, obesity, NASH, NAFLD, nephrotic syndrome, chronic renal failure, insulin resistance, diabetes, metabolic syndrome X, impaired glucose tolerance, hyperlipidemia, coronary heart disease, thyroid disease, thyroid cancer, depression, glaucoma, cardiac arrhythmias, heart failure, or osteoporosis.

[0243] Also provided are compounds that selectively distribute to the liver. In one embodiment, the compounds have at least 10 fold, 25 fold, 50 fold, 75 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, 1000 fold, 2000 fold, 3000 fold, 4000 fold, 5000 fold 6000 fold, 7000 fold, 8000 fold, 9000 fold, 10,000 fold, 20,000 fold, 30,000 fold, 40,000 fold or 50,000 fold greater selectivity. In one embodiment the selectivity for the liver is compared to the heart. In another embodiment the selectivity for the liver is compared to the pituitary. In another embodiment the selectivity for the liver is compared to the kidney.

[0244] Also provided are phosphinic acid-containing T3 mimetics or prodrug thereof that have improved liver selectivity as compared to a corresponding compound where the phosphorus-containing group is replaced with a carboxylic acid, but wherein the corresponding compound is otherwise identical. In one embodiment, the phosphinic acid-containing compound (or prodrug thereof) has at least 10 fold, 25 fold, 50 fold, 75 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, 1000 fold, 2000 fold, 3000 fold, 4000 fold, 5000 fold 6000 fold, 7000 fold, 8000 fold, 9000 fold, 10,000 fold, 20,000 fold, 30,000 fold, 40,000 fold or 50,000 fold greater selectivity for the liver as compared to the corresponding carboxylic acid compound. In one embodiment the liver selectivity is relative to the heart. In another embodiment the liver selectivity is relative to the kidney. In another embodiment the liver selectivity is relative to the pituitary.

[0245] Also provided are phosphinic acid-containing T3 mimetics or prodrug thereof that have a decreased Ki as compared to a corresponding compound where the phosphorus-containing group is replaced with a carboxylic acid, but wherein the corresponding compound is otherwise identical. In one embodiment, the phosphinic acid-containing compound has at least 2 fold, 5 fold, 7 fold, 10 fold, 25 fold, or 50 fold lower Ki than the corresponding carboxylic acid derivative compound (wherein Ki is measured relative to T3). In another embodiment, the Ki of the phosphinic acid-containing compound is $\leq$ 150 nM $\leq$ 100 nM, $\leq$ 90nM, $\leq$ 80nM, $\leq$70nM, $\leq$ 60nM, $\leq$ 50nM, $\leq$ 40nM, $\leq$ 30nM, relative to T3. For purposes of clarity, it is noted that binding affinity increases as the numerical value of Ki decreases, *i.e.*, there is an inverse relationship between Ki and binding affinity. In another embodiment the phosphinic acid-containing compound has the same Ki as the corresponding carboxylic acid derivative. In another embodiment the phosphinic acid-containing compound has a greater Ki than the corresponding carboxylic acid derivative.

[0246] Also provided are compounds of the present invention that bind at least one thyroid hormone receptor with an Ki of $\leq$ 100 nM, $\leq$ 90nM, $\leq$ 80nM, $\leq$70nM, $\leq$ 60nM, $\leq$ 50nM, $\leq$ 40nM, $\leq$ 30nM, $\leq$ 20nM, $\leq$ 10nM,

≤ 50nM, ≤1nM, or ≤ 0.5nM relative to T3. In one embodiment said thyroid hormone receptor is TRα. In one embodiment said thyroid hormone receptor is TRβ. Also provided are compounds that bind at least one thyroid hormone receptor with an Ki of ≥ 100 nM, ≥ 90nM, ≥ 80nM, ≥70nM, ≥ 60nM, ≥ 50nM, ≥ 40nM, ≥ 30nM, ≥ 20nM, ≥ 10nM, ≥ 50nM, ≥1nM, or ≥ 0.5nM relative to T3, but in each case ≤ 150nM. In one embodiment said thyroid hormone receptor is TRα. In one embodiment said thyroid hormone receptor is TRβ. In one embodiment said thyroid hormone receptor is TRα1. In one embodiment said thyroid hormone receptor is TRβ1. In one embodiment said thyroid hormone receptor is TRα2. In one embodiment said thyroid hormone receptor is TRβ2.

[0247] Novel methods described herein describe the use of phosphinic acid-containing compounds that bind to TRs. In one aspect, novel compounds described below include compounds of Formula I, II, III, VIII, X, XVI, and XVII. The compounds of the present invention can be used in the methods described herein.

Novel Compounds of the Invention

[0248] The novel compounds of the invention are phosphinic acid-containing compounds that bind to and activate thyroid receptors in the liver. The present invention relates to compounds of Formula I, II, III, VIII, X, XVI, and XVII, including stereoisomers and mixtures of stereoisomers thereof, pharmaceutically acceptable salts thereof, co-crystals thereof, and prodrugs (including stereoisomers and mixtures of stereoisomers thereof) thereof, and pharmaceutically acceptable salts and co-crystals of the prodrugs.

[0249] Importantly, lower alkyl esters of phosphinic acid are not prodrug moieties as the phosphoester bond is not cleaved *in vivo*. Thus, the lower alkyl esters of phosphinic acid-containing compounds of the invention are not themselves prodrugs. The compounds can be made into prodrugs as disclosed above.

[0250] The compounds of the present invention may be either crystalline, amorphous or a mixture thereof. Compositions comprising a crystalline form a compound of the present invention may contain only one crystalline form of said compound or more than one crystalline form. For example, the composition may contain two or more different polymorphs. The polymorphs may be two different polymorphs of the free form, two or more polymorphs of different co-crystal forms, two or more polymorphs of different salt forms, a combination of one or more polymorphs of one or more co-crystal forms and one or more polymorphs of the free form, a combination of one or more polymorphs of one or more salt forms and one or more polymorphs of the free form, or a combination of one or more polymorphs of one or more co-crystal forms and one or more polymorphs of one or more salt forms.

[0251] Pharmaceutically acceptable base addition salts of the compounds herein are included in the present invention. Pharmaceutically acceptable base addition salts refer to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, zinc, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like.

[0252] Pharmaceutically acceptable acid addition salts of the compounds herein having a base functional group (*e.g.*, a prodrug whereby the

phosphorus-containing group is protected with a group comprising a base functional group) are also included in the present invention. Pharmaceutically acceptable acid addition salts refer to those salts which retain the biological effectiveness and properties of the free base, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic acid or an organic acid to the free base. Salts derived from inorganic acids include, but are not limited to, acistrate, hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, besylate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate. bromide, fumarate, pamoate, glucouronate, hydroiodide, iodide, sulfate, xinofoate and chloride salts

[0253] The compounds of the present invention may be pure or substantially pure or have a purity of at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or purity at least 99.5%. The compounds may also be part of a pharmaceutically acceptable composition. The compounds may also be part of a biological material or sample. Thus, included in the present invention are cells and tissues comprising a compound of the present invention. The cells or tissues can be *in vivo*, *ex vivo* or *in vitro*. Examples include liver or liver cells (*e.g.*, hepatocytes), blood, gastric fluid (simulated or actual), intestinal fluid (simulated or actual), and urine.

[0254] In one aspect the invention relates to a phosphinic acid-containing thyromimetic compound of Formula X:

(Ar^1)-G-(Ar^2)-T-X

wherein:

Ar^1 and Ar^2 are aryl groups;

G is an atom or group of atoms that links Ar^1 and Ar^2 through a single C, S, Se, O, or N atom or CH_2 linked to C, S, Se, O, or N, wherein the C or N is substituted;

T is an atom or group of atoms linking Ar^2 to X through 1-4 contiguous atoms or is absent;

X is a phosphinic acid, or a prodrug thereof.

[0255] In one embodiment the compound has a Ki ≤ 150nM. Another embodiment includes a pharmaceutical composition comprising the compound and a at least one excipient. In another embodiment the pharmaceutical composition has a bioavailability of at least 15%. In another embodiment the compound is crystalline. In another embodiment the pharmaceutical composition is a unit dose.

[0256] In another aspect the invention relates to a method of improving liver versus heart selectivity or for increasing the therapeutic index of a thyromimetic compound of Formula Y:

$$(Ar^1)\text{-}G\text{-}(Ar^2)\text{-}T\text{-}E$$

wherein:

Ar^1, Ar^2, and G are defined as above;

T is an atom or group of atoms linking Ar^2 to E through 1-4 contiguous atoms or is absent;

E is a functional group or moiety with a pKa ≤ 7.4, is carboxylic acid (COOH) or esters thereof, sulfonic acid, tetrazole, hydroxamic acid, 6-azauracil, thiazolidinedione, acylsulfonamide, or other carboxylic acid surrogates known in the art or a prodrug thereof, or an atom or group of atoms containing an O or N that binds the thyroid hormone binding pocket of a TRα or TRβ, but wherein E is not a phosphonic acid or phosphinic acid or ester thereof;

comprising the step of replacing E with a phosphinic acid or a prodrug thereof. In one embodiment the compound has a Ki ≤ 150nM. Another embodiment includes a pharmaceutical composition comprising the compound and a at least one excipient. In another embodiment the pharmaceutical composition has a bioavailability of at least 15%. In another embodiment the compound is crystalline. In another embodiment the pharmaceutical composition is a unit dose.

[0257] In another aspect the invention relates to a method of designing a thyromimetic compound with improved liver versus heart selectivity or improved therapeutic index comprising the steps of:

obtaining a formula for a thyromimetic of Formula Y:

(Ar^1)-G-(Ar^2)-T-E

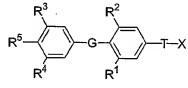
wherein:

Ar^1, Ar^2, G, and E are defined as above;

T is an atom or group of atoms linking Ar^2 to E through 1-4 contiguous atoms or is absent;

comprising the step of replacing E with a phosphinic acid or a prodrug thereof; and synthesizing a compound of Formula X wherein X is phosphinic acid or a prodrug thereof. In one embodiment the compound has a Ki ≤ 150nM. Another embodiment includes a pharmaceutical composition comprising the compound and a at least one excipient. In another embodiment the pharmaceutical composition has a bioavailability of at least 15%. In another embodiment the compound is crystalline. In another embodiment the pharmaceutical composition is a unit dose.

[0258] In one aspect, the invention relates to a compound of Formula I:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, $-S(=O)_2-$, $-CH_2-$, $-CF_2-$, -CHF-, -C(O)-, -CH(OH)-, -NH-, and $-N(C_1-C_4$ alkyl)-, or CH_2 linked to any of the preceding groups;

or G is R^{50}-R^{51} wherein;

R^{50}-R^{51} together are $-C(R^{52})=C(R^{52})-$ or alternatively R^{50} and R^{51} are independently selected from O, S and $-CH(R^{53})-$, with the provisos that at least one R^{50} and R^{51} is $-CH(R^{53})-$, and when one of R^{50} and R^{51} is O or S, then R^{53} is R^{54};

R^{54} is hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl,

difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R^{52} is selected from hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of $-(CR^a_2)_k-$, $-CR^b=CR^b-(CR^a_2)_n-$, $-(CR^a_2)_n-CR^b=CR^b-$, $-(CR^a_2)-CR^b=CR^b-(CR^a_2)-$, $-O(CR^b_2)(CR^a_2)_n-$, $-S(CR^b_2)(CR^a_2)_n-$, $-N(R^c)(CR^b_2)(CR^a_2)_n-$, $-N(R^b)C(O)(CR^a_2)_n-$, $-(CR^a_2)_mC(R^b)(NR^bR^c)-$, $-C(O)(CR^a_2)_m-$, $-(CR^a_2)_mC(O)-$, $-(CR^b_2)-O-(CR^b_2)-(CR^a_2)_p-$, $-(CR^b_2)-S-(CR^b_2)-(CR^a_2)_p-$, $-(CR^b_2)-N(R^c)-(CR^b_2)-(CR^a_2)_p-$, $-(CR^a_2)_p-(CR^b_2)-O-(CR^b_2)-$, $-(CR^a_2)_p-(CR^b_2)-S-(CR^b_2)-$, $-(CR^a_2)_p-(CR^b_2)-N(R^c)-(CR^b_2)-$ and $-(CH_2)_pC(O)N(R^b)C(R^a_2)-$;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted $-C_1$-C_4 alkyl, halogen, -OH, optionally substituted $-O-C_1$-C_4 alkyl, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-S-C_1$-C_4 alkyl, $-NR^bR^c$, optionally substituted $-C_2$-C_4 alkenyl, and optionally substituted $-C_2$-C_4 alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^b is independently selected from the group consisting of hydrogen and optionally substituted $-C_1$-C_4 alkyl;

Each R^c is independently selected from the group consisting of hydrogen, optionally substituted $-C_1$-C_4 alkyl, optionally substituted $-C(O)-C_1$-C_4 alkyl, and -C(O)H;

R^1 and R^2 are each independently selected from the group consisting of halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted -O-C_1-C_3 alkyl, and cyano;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyano, optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted $-(CR^a_2)_m$aryl, optionally substituted $-(CR^a_2)_m$cycloalkyl, optionally substituted $(CR^a_2)_m$heterocycloalkyl, $-C(R^b)=C(R^b)$-aryl, $-C(R^b)=C(R^b)$-cycloalkyl, $-C(R^b)=C(R^b)$-heterocycloalkyl, $-C\equiv C$(aryl), $-C\equiv C$(cycloalkyl), $-C\equiv C$(heterocycloalkyl), $-(CR^a_2)_n(CR^b_2)NR^fR^g$, $-OR^d$, $-SR^d$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, $-C(O)NR^fR^g$, $-C(O)OR^h$, $-C(O)R^e$, $-N(R^b)C(O)R^e$, $-N(R^b)C(O)NR^fR^g$, $-N(R^b)S(=O)_2R^e$, $-N(R^b)S(=O)_2NR^fR^g$, and $-NR^fR^g$;

Each R^d is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, optionally substituted $-(CR^b_2)_n$heterocycloalkyl, and $-C(O)NR^fR^g$;

Each R^e is optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted $-(CR^a_2)_n$aryl, optionally substituted $-(CR^a_2)_n$cycloalkyl, and optionally substituted $-(CR^a_2)_n$heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, and optionally substituted $-(CR^b_2)_n$heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group of O, NR^e, and S, wherein said optionally substituted heterocyclic ring

may be substituted with 0-4 substituents selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$;

Each R^h is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally substituted -$(CR^b_2)_n$cycloalkyl, and optionally substituted -$(CR^b_2)_n$heterocycloalkyl;

R^5 is selected from the group consisting of -OH, optionally substituted -OC_1-C_6 alkyl, -$OC(O)R^e$, -$OC(O)OR^h$, -$NHC(O)OR^h$, -$OC(O)NH(R^h)$, -F, -$NHC(O)R^e$, -$NHS(=O)R^e$, -$NHS(=O)_2R^e$, -$NHC(=S)NH(R^h)$, and -$NHC(O)NH(R^h)$; or

R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^5 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is $P(O)(YR^{11})Y''$;

Y'' is selected from the group consisting of hydrogen, optionally substituted -C_1-C_6-alkyl, -CF_3, -CHF_2, -CH_2F, -CH_2OH, optionally substituted -C_2-C_6 alkenyl, optionally substituted -C_2-C_6 alkynyl, optionally substituted -$(CR^a_2)_n$cycloalkyl, optionally substituted -$(CR^a_2)_n$heterocycloalkyl, -$(CR^a_2)_kS(=O)R^e$, -$(CR^a_2)_kS(=O)_2R^e$, -$(CR^a_2)_kS(=O)_2NR^fR^g$, -$(CR^a_2)_kC(O)NR^fR^g$, and -$(CR^a_2)_kC(O)R^e$;

Y is selected from the group consisting of -O-, and -NR^v-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -$C(R^z)_2OC(O)NR^z_2$, -NR^z-C(O)-R^y, -$C(R^z)_2$-$OC(O)R^y$,

$-C(R^z)_2$-O-C(O)OR^y, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^v$-, then R^{11} attached to $-NR^v$- is selected from the group consisting of -H, $-[C(R^z)_2]_q$-C(O)R^y, $-C(R^x)_2C(O)OR^y$, $-[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

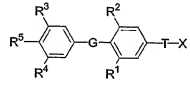
Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cycloalkyl group;

Each R^v is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0259] In another aspect, the invention relates to a compound of Formula I:



wherein:

G, T, k, m, n, p, R^a, R^b, R^c, R^1, R^2, R^3, R^4, R^d, R^e, R^f, R^g, R^h R^5, X, Y'', q, R^z, R^y, R^x, and R^v are defined as above;

Y is selected from the group consisting of -O-, and $-NR^v$-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z{}_2$, $-NR^z$-C(O)-R^y, $-C(R^z)_2$-OC(O)R^y, $-C(R^z)_2$-O-C(O)OR^y, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

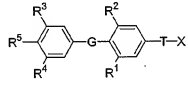
when Y is -NR^v-, then R^{11} attached to -NR^v- is selected from the group consisting of -H, -$[C(R^z)_2]_q$-C(O)OR^y, -$C(R^x)_2C(O)OR^y$, -$[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

with the proviso that:

a) when G is -O-, T is -CH_2-, R^1 and R^2 are each chloro, R^3 is phenyl, R^4 is hydrogen, and R^5 is –OH, then X is not P(O)(OH)CH_3 or P(O)(OCH_2CH_3)(CH_3);

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0260] In a further aspect, the invention relates to a compound of Formula I:



wherein:

G, T, k, m, n, p, R^a, R^b, R^c, R^1, R^2, R^3, R^4, R^d, R^e, R^f, R^g, R^h R^5, X, Y'', q, R^z, R^y, R^x, and R^v are defined as above;

Y is selected from the group consisting of -O-, and -NR^v-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -$C(R^z)_2OC(O)NR^z_2$, -NR^z-C(O)-R^y, -$C(R^z)_2$-$OC(O)R^y$, -$C(R^z)_2$-O-C(O)OR^y, -$C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR^v-, then R^{11} attached to -NR^v- is selected from the group consisting of -H, -$[C(R^z)_2]_q$-C(O)OR^y, -$C(R^x)_2C(O)OR^y$, -$[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

with the proviso that:

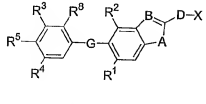
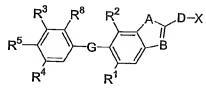
a) when G is -O-, -S-, -Se-, -S(=O)-, -$S(=O)_2$-, -CH_2-, -C(O)-, -NH- and, T is -$(CH_2)_{0-4}$- or -C(O)NH(CR^b_2)-, R^1 and R^2 are

independently chosen from the group consisting of hydrogen, halogen, -C_1-C_4 alkyl, R^3 is -$C(O)NR^{25}R^{26}$, -CH_2-$NR^{25}R^{26}$, -NR^{25}-$C(O)R^{26}$, -OR^{27}, R^{28}, or  , R^4 is hydrogen, halogen, cyano or alkyl, and R^5 is -OH, R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, cycloalkyl, aralkyl or heteroaralkyl, R^{27} is aryl, heteroaryl, alkyl, aralkyl, or heteroaralkyl, R^{28} is aryl, heteroaryl, or cycloalkyl, R^{29} is hydrogen, aryl, heteroaryl, alkyl, aralkyl, heteroaralkyl, then X is not –P(O)(OH)C_1-C_6 alkyl or –P(O)(O-lower alkyl)C_1-C_6 alkyl;

b) when G is -O-, -S-, -Se-, -S(=O)-, -$S(=O)_2$-, -CH_2-, -CF_2-, -C(O)-, -NH- and, T is -$C(O)NH(CR^b_2)$-, R^1 and R^2 are independently halogen, cyano, -C_1-C_4 alkyl, R^3 is halogen, -C_1-C_6 alkyl, -C_2-C_6 alkynyl, -C_4-C_7 cycloalkenyl, -C_3-C_7 cycloalkoxy, -$S(=O)_2(NR^{14}R^{15})$, -$N(R^{16})S(=O)_2R^{17}$, -SR^{17}, -$S(=O)R^{17}$, -$S(=O)_2R^{17}$, -$C(O)R^{16}$, or -$CR^{18}(OR^{16})R^{19}$, R^4 is halogen, cyano or alkyl, and R^5 is -OH, optionally substituted -OC_1-C_6 alkyl, aroyl or alkanoyl, R^{14}, R^{15}, R^{16}, R^{18} and R^{19} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, or R^{14} and R^{15} may be joined so as to comprise a chain of 3 to 6 methylene groups to form a ring of 4 to 7-membered in size, R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, then X is not –P(O)(OH)C_1-C_6 alkyl or –P(O)(O-lower alkyl)C_1-C_6 alkyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0261] In one aspect, the invention relates to a compound of Formula II:

 or 

wherein:

A is selected from the group consisting of -NR^i-, -O-, and -S-;

B is selected from the group consisting of –CR^b-, and -N-;

R^i is selected from the group consisting of hydrogen, -C(O)C_1-C_4 alkyl, and -C_1-C_4 alkyl;

R^b is selected from the group consisting of hydrogen and optionally substituted -C_1-C_4 alkyl;

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)$_2$-, -CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C_1-C_4 alkyl)-, or CH_2 linked to any of the preceding groups;

or G is R^{50}-R^{51} wherein;

R^{50}-R^{51} together are –C(R^{52})=C(R^{52})- or alternatively R^{50} and R^{51} are independently selected from O, S and –CH(R^{53})-, with the provisos that at least one R^{50} and R^{51} is –CH(R^{53})-, and when one of R^{50} and R^{51} is O or S, then R^{53} is R^{54};

R^{54} is hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

R^{52} is selected from hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

D is selected from the group consisting of a bond, -(CR^a_2)-, and -C(O)-;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_4 alkyl, halogen, -OH, optionally substituted -O-C_1-C_4 alkyl, -OCF_3, -$OCHF_2$, -OCH_2F, optionally substituted -S-C_1-C_4 alkyl, -NR^bR^c, optionally substituted -C_2-C_4 alkenyl, and optionally substituted -C_2-C_4 alkynyl; with the proviso that when one R^a is

attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^c is independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -C(O)-C_1-C_4 alkyl, and -C(O)H;

R^1 and R^2 are each independently selected from the group consisting of halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted -O-C_1-C_3 alkyl, and cyano;

R^8 is selected from the group consisting of hydrogen, halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted -O-C_1-C_3 alkyl, hydroxy, -(CR^a_2)aryl, -(CR^a_2)cycloalkyl, -(CR^a_2)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyano, optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^a_2)_m$aryl, optionally substituted -$(CR^a_2)_m$cycloalkyl, optionally substituted -$(CR^a_2)_m$heterocycloalkyl, $-C(R^b)=C(R^b)$-aryl, $-C(R^b)=C(R^b)$-cycloalkyl, $-C(R^b)=C(R^b)$-heterocycloalkyl, -C≡C(aryl), -C≡C(cycloalkyl), -C≡C(heterocycloalkyl), $-(CR^a_2)_n(CR^b_2)NR^fR^g$, $-OR^d$, $-SR^d$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, $-C(O)NR^fR^g$, $-C(O)OR^h$, $-C(O)R^e$, $-N(R^b)C(O)R^e$, $-N(R^b)C(O)NR^fR^g$, $-N(R^b)S(=O)_2R^e$, $-N(R^b)S(=O)_2NR^fR^g$, and $-NR^fR^g$;

Each R^d is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally

substituted -$(CR^b_2)_n$cycloalkyl, optionally substituted -$(CR^b_2)_n$heterocycloalkyl, and -$C(O)NR^fR^g$;

Each R^c is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^a_2)_n$aryl, optionally substituted -$(CR^a_2)_n$cycloalkyl, and optionally substituted -$(CR^a_2)_n$heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally substituted -$(CR^b_2)_n$cycloalkyl, and optionally substituted -$(CR^b_2)_n$heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O, NR^e, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted optionally substituted phenyl, and -$C(O)OR^h$;

Each R^h is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally substituted -$(CR^b_2)_n$cycloalkyl, and optionally substituted -$(CR^b_2)_n$heterocycloalkyl; or

R^3 and R^8 are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^8 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R^8 and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R^5 is selected from the group consisting of -OH, optionally substituted $-OC_1-C_6$ alkyl, $-OC(O)R^e$, $-OC(O)OR^h$, $-NHC(O)OR^h$, $-OC(O)NH(R^h)$, -F, $-NHC(O)R^e$, $-NHS(=O)R^e$, $-NHS(=O)_2R^e$, $-NHC(=S)NH(R^h)$, and $-NHC(O)NH(R^h)$; or

R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^5 are attached, including 0 to 2 heteroatoms independently selected from $-NR^h-$, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is $P(O)(YR^{11})Y''$;

Y'' is selected from the group consisting of hydrogen, optionally substituted $-C_1-C_6$-alkyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2OH$, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-(CR^a_2)_n$cycloalkyl, optionally substituted $(CR^a_2)_n$heterocycloalkyl, $-(CR^a_2)_kS(=O)R^e$, $-(CR^a_2)_kS(=O)_2R^e$, $-(CR^a_2)_kS(=O)_2NR^fR^g$, $-(CR^a_2)_kC(O)NR^fR^g$, and $-(CR^a_2)_kC(O)R^e$;

Y is selected from the group consisting of -O-, and $-NR^v-$;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z_2$, $-NR^z-C(O)-R^y$, $-C(R^z)_2-OC(O)R^y$, $-C(R^z)_2-O-C(O)OR^y$, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^v-$, then R^{11} attached to $-NR^v-$ is selected from the group consisting of -H, $-[C(R^z)_2]_q-C(O)OR^y$, $-C(R^z)_2C(O)OR^y$, $-[C(R^z)_2]_q-C(O)SR^y$, and -cycloalkylene-$C(O)OR^y$;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

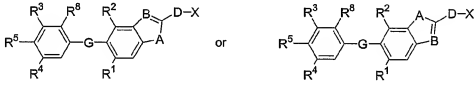
Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cycloalkyl group;

Each R^v is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0262] In another aspect, the invention relates to a compound of Formula II:



wherein:

A, B, R^i, R^b, G, D, R^a, R^1, R^2, R^8, R^3, R^4, R^d, R^e, R^f, R^g, R^h, R^5, X, Y'', q, R^z, R^y, R^x, and R^v are as defined above;

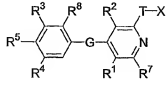
Y is selected from the group consisting of -O-, and -NR^v-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -$C(R^z)_2OC(O)NR^z_2$, -NR^z-C(O)-R^y, -$C(R^z)_2$-OC(O)R^y, -$C(R^z)_2$-O-C(O)OR^y, -$C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR^v-, then R^{11} attached to -NR^v- is selected from the group consisting of -H, -$[C(R^z)_2]_q$-C(O)OR^y, -$C(R^x)_2$C(O)OR^y, -$[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0263] In another aspect, the invention relates to a compound of Formula III:



wherein

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)$_2$-, -CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C_1-C_4 alkyl)-, or CH_2 linked to any of the preceding groups;

or G is R^{50}-R^{51} wherein;

R^{50}-R^{51} together are –C(R^{52})=C(R^{52})- or alternatively R^{50} and R^{51} are independently selected from O, S and –CH(R^{53})-, with the provisos that at least one R^{50} and R^{51} is –CH(R^{53})-, and when one of R^{50} and R^{51} is O or S, then R^{53} is R^{54};

R^{54} is hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R^{52} is selected from hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of -(CR^a_2)$_k$-, -CR^b=CR^b-(CR^a_2)$_n$-, -(CR^a_2)$_n$-CR^b=CR^b-, -(CR^a_2)-CR^b=CR^b-(CR^a_2)-, -O(CR^b_2)(CR^a_2)$_n$-, -S(CR^b_2)(CR^a_2)$_n$-, -N(R^c)(CR^b_2)(CR^a_2)$_n$-, -N(R^b)C(O)(CR^a_2)$_n$-, -(CR^a_2)$_m$C(R^b)(NR^bR^c)-, -C(O)(CR^a_2)$_m$-, -(CR^a_2)$_m$C(O)-, -(CR^b_2)-O-(CR^b_2)-(CR^a_2)$_p$-, -(CR^b_2)-S-(CR^b_2)-(CR^a_2)$_p$-, -(CR^b_2)-N(R^c)-(CR^b_2)-(CR^a_2)$_p$-, -(CR^a_2)$_p$-(CR^b_2)-O-(CR^b_2)-,

$-(CR^a_2)_p-(CR^b_2)-S-(CR^b_2)-$, $-(CR^a_2)_p-(CR^b_2)-N(R^c)-(CR^b_2)-$
$-(CH_2)_pC(O)N(R^b)C(R^a_2)-$, $-(CR^a_2)_nC(R^b_2)O-$,
$-(CR^a_2)_nC(R^b_2)N(R^b)-$, $-(CR^a_2)_nC(R^b_2)S-$, $-C(O)(CR^a_2)_pC(R^b_2)O-$,
$-C(O)(CR^a_2)_pC(R^b_2)N(R^b)-$, $-C(O)(CR^a_2)_pC(R^b_2)S-$, $-(CR^a_2)_pC(O)C(R^b_2)O-$,
$-(CR^a_2)_pC(O)C(R^b_2)N(R^b)-$, and $-(CR^a_2)pC(O)C(R^b_2)S-$;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_4$ alkyl, halogen, -OH, optionally substituted $-O-C_1-C_4$ alkyl, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-S-C_1-C_4$ alkyl, $-NR^bR^c$, optionally substituted $-C_2-C_4$ alkenyl, and optionally substituted $-C_2-C_4$ alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^b is independently selected from the group consisting of hydrogen and optionally substituted $-C_1-C_4$ alkyl;

Each R^c is independently selected from the group consisting of hydrogen and optionally substituted $-C_1-C_4$ alkyl, optionally substituted $-C(O)-C_1-C_4$ alkyl, and -C(O)H;

R^1 and R^2 are each independently selected from the group consisting of halogen, optionally substituted $-C_1-C_4$ alkyl, optionally substituted $-S-C_1-C_3$ alkyl, optionally substituted $-C_2-C_4$ alkenyl, optionally substituted $-C_2-C_4$ alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-O-C_1-C_3$ alkyl, and cyano;

R^8 is selected from the group consisting of hydrogen, halogen, optionally substituted $-C_1-C_4$ alkyl, optionally substituted $-S-C_1-C_3$ alkyl, optionally substituted $-C_2-C_4$ alkenyl, optionally substituted $-C_2-C_4$ alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-O-C_1-C_3$ alkyl, hydroxy, $-(CR^a_2)$aryl, $-(CR^a_2)$cycloalkyl,

-(CR^a_2)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyano, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted -(CR^a_2)$_m$aryl, optionally substituted -(CR^a_2)$_m$cycloalkyl, optionally substituted -(CR^a_2)$_m$heterocycloalkyl, -C(R^b)=C(R^b)-aryl, -C(R^b)=C(R^b)-cycloalkyl, -C(R^b)=C(R^b)-heterocycloalkyl, -C≡C(aryl), -C≡C(cycloalkyl), -C≡C(heterocycloalkyl), -(CR^a_2)$_n$(CR^b_2)NR^fR^g, $-OR^d$, $-SR^d$, -S(=O)R^e, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, -C(O)NR^fR^g, -C(O)OR^h, -C(O)R^e, -N(R^h)C(O)R^e, -N(R^b)C(O)NR^fR^g, -N(R^b)S(=O)$_2R^e$, -N(R^b)S(=O)$_2NR^fR^g$, and $-NR^fR^g$;

Each R^d is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted -(CR^b_2)$_n$aryl, optionally substituted -(CR^b_2)$_n$cycloalkyl, optionally substituted -(CR^b_2)$_n$heterocycloalkyl, and -C(O)NR^fR^g;

Each R^e is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted -(CR^a_2)$_n$aryl, optionally substituted -(CR^a_2)$_n$cycloalkyl, and optionally substituted -(CR^a_2)$_n$heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted -(CR^b_2)$_n$aryl, optionally substituted -(CR^b_2)$_n$cycloalkyl, and optionally substituted -(CR^b_2)$_n$heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O, NR^e, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the

group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^b$;

Each R^h is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally substituted -$(CR^b_2)_n$cycloalkyl, and optionally substituted -$(CR^b_2)_n$heterocycloalkyl; or

R^3 and R^8 are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^8 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R^8 and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R^5 is selected from the group consisting of -OH, optionally substituted -OC_1-C_6 alkyl, -$OC(O)R^e$, -$OC(O)OR^h$, -$NHC(O)OR^h$, -$OC(O)NH(R^h)$, -F, -$NHC(O)R^e$, -$NHS(=O)R^e$, -$NHS(=O)_2R^e$, -$NHC(=S)NH(R^h)$, and -$NHC(O)NH(R^h)$; or

R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^5 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

R^7 is selected from the group consisting of hydrogen, halogen, amino, hydroxyl, -OCF_3, -$OCHF_2$, -OCH_2F, -CF_3, -CHF_2, -CH_2F, cyano, -O-C_1-C_4 alkyl, -SH and -S-C_1-C_4 alkyl;

X is $P(O)(YR^{11})Y''$;

Y'' is selected from the group consisting of hydrogen, optionally substituted $-C_1-C_6$-alkyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2OH$, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-(CR^a_2)_n$cycloalkyl, optionally substituted $(CR^a_2)_n$heterocycloalkyl, $-(CR^a_2)_kS(=O)R^e$, $-(CR^a_2)_kS(=O)_2R^e$, $-(CR^a_2)_kS(=O)_2NR^fR^g$, $-(CR^a_2)_kC(O)NR^fR^g$, and $-(CR^a_2)_kC(O)R^e$;

Y is selected from the group consisting of -O-, and $-NR^v$-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z_2$, $-NR^z$-C(O)-R^y, $-C(R^z)_2$-$OC(O)R^y$, $-C(R^z)_2$-O-C(O)OR^y, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^v$-, then R^{11} attached to $-NR^v$- is selected from the group consisting of -H, $-[C(R^z)_2]_q$-C(O)OR^y, $-C(R^x)_2C(O)OR^y$, $-[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

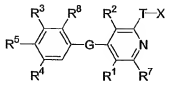
Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cycloalkyl group;

Each R^v is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

In another aspect, the invention relates to a compound of Formula III:



wherein

G, T, k, m, n, p, R^a, R^b, R^c, R^1, R^2, R^8 R^3, R^4, R^d, R^e, R^f, R^g, R^h, R^5, R^7, X, Y'', q, R^z, R^y, R^x, and R^v are as described above;

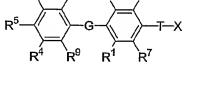
Y is selected from the group consisting of -O-, and -NR^v-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -$C(R^z)_2OC(O)NR^z_2$, -NR^z-C(O)-R^y, -$C(R^z)_2$-OC(O)R^y, -$C(R^z)_2$-O-C(O)OR^y, -$C(R^x)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR^v-, then R^{11} attached to -NR^v- is selected from the group consisting of -H, -$[C(R^z)_2]_q$-C(O)OR^y, -$C(R^x)_2$C(O)OR^y, -$[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0264] In one aspect, the invention relates to a compound of Formula VIII:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -$S(=O)_2$-, -Se-, -CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -CH(C_1-C_4 alkyl)-, -CH(C_1-C_4 alkoxy)-, -C(=CH_2)-,-NH-, and -N(C_1-C_4 alkyl)-, or CH_2 linked to any of the preceding groups;

or G is R^{50}-R^{51} wherein;

R^{50}-R^{51} together are $-C(R^{52})=C(R^{52})-$ or alternatively R^{50} and R^{51} are independently selected from O, S and $-CH(R^{53})-$, with the provisos that at least one R^{50} and R^{51} is $-CH(R^{53})-$, and when one of R^{50} and R^{51} is O or S, then R^{53} is R^{54};

R^{54} is hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R^{52} is selected from hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of $-(CR^a_2)_k-$, $-CR^b=CR^b-(CR^a_2)_n-$, $-(CR^a_2)_n-CR^b=CR^b-$, $-(CR^a_2)-CR^b=CR^b-(CR^a_2)-$, $-O(CR^b_2)(CR^a_2)_n-$, $-S(CR^b_2)(CR^a_2)_n-$, $-N(R^c)(CR^b_2)(CR^a_2)_n-$, $-N(R^b)C(O)(CR^a_2)_n-$, $-(CR^a_2)_mC(R^b)(NR^bR^c)-$, $-C(O)(CR^a_2)_m-$, $-(CR^a_2)_mC(O)-$, $-(CR^b_2)-O-(CR^b_2)-(CR^a_2)_p-$, $-(CR^b_2)-S-(CR^b_2)-(CR^a_2)_p-$, $-(CR^b_2)-N(R^c)-(CR^b_2)-(CR^a_2)_p-$, $-(CR^a_2)_p-(CR^b_2)-O-(CR^b_2)-$, $-(CR^a_2)_p-(CR^b_2)-S-(CR^b_2)-$, $-(CR^a_2)_p-(CR^b_2)-N(R^c)-(CR^b_2)-$ $-C(O)N(R^b)(CR^b_2)(CR^a_2)_p-$, and $-(CH_2)_pC(O)N(R^b)C(R^a_2)-$;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted $-C_1$-C_4 alkyl, halogen, -OH, optionally substituted $-O-C_1$-C_4 alkyl, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-S-C_1$-C_4 alkyl, $-NR^bR^c$, optionally substituted $-C_2$-C_4 alkenyl, and optionally substituted $-C_2$-C_4 alkynyl; with the proviso that when one R^a is

attached to C through an O, S, or N atom, then the other R^e attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^b is independently selected from the group consisting of hydrogen and optionally substituted -C_1-C_4 alkyl;

Each R^c is independently selected from the group consisting of hydrogen and optionally substituted -C_1-C_4 alkyl, optionally substituted -C(O)-C_1-C_4 alkyl, and -C(O)H;

R^1, R^2, R^6, and R^7 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, optionally substituted -O-C_1-C_3 alkyl, and cyano; with the proviso that at least one of R^1 and R^2 is not hydrogen;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, optionally substituted -O-C_1-C_3 alkyl, hydroxy, -(CR^a_2)aryl, -(CR^a_2)cycloalkyl, -(CR^a_2)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano; or

R^6 and T are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations including 0 to 2 heteroatoms independently selected from –NR^i-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by –(CR^a_2)- or –C(O)- bonded to a ring carbon or a ring nitrogen;

R^i is selected from the group consisting of hydrogen, -C(O)C_1-C_4 alkyl, and -C_1-C_4 alkyl; or

R^1 and R^7 are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2

unsaturations, not including the unsaturation on the ring to which R^1 and R^7 are attached, including 0 to 2 heteroatoms independently selected from $-NR^b-$, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyano, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^a_2)_m$aryl, optionally substituted $-(CR^a_2)_m$cycloalkyl, optionally substituted $-(CR^a_2)_n$heterocycloalkyl, $-C(R^b)=C(R^b)$-aryl, $-C(R^b)=C(R^b)$-cycloalkyl, $-C(R^b)=C(R^b)$-heterocycloalkyl, $-C\equiv C$(aryl), $-C\equiv C$(cycloalkyl), $-C\equiv C$(heterocycloalkyl), $-(CR^a_2)_n(CR^b_2)NR^fR^g$, $-OR^d$, $-SR^d$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, $-C(O)NR^fR^g$, $-C(O)OR^h$, $-C(O)R^e$, $-N(R^b)C(O)R^e$, $-N(R^b)C(O)NR^fR^g$, $-N(R^b)S(=O)_2R^e$, $-N(R^b)S(=O)_2NR^fR^g$, and $-NR^fR^g$;

Each R^d is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, optionally substituted $-(CR^b_2)_n$heterocycloalkyl, and $-C(O)NR^fR^g$;

Each R^e is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^a_2)_n$aryl, optionally substituted $-(CR^a_2)_n$cycloalkyl, and optionally substituted $-(CR^a_2)_n$heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, and optionally substituted $-(CR^b_2)_n$heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4

unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O, NR^e, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted $-C_1-C_4$ alkyl, $-OR^b$, oxo, cyano, $-CF_3$, $-CHF_2$, $-CH_2F$, optionally substituted phenyl, and $-C(O)OR^h$;

Each R^h is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, and optionally substituted $-(CR^b_2)_n$heterocycloalkyl; or

R^3 and R^8 are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^8 are attached, including 0 to 2 heteroatoms independently selected from $-NR^h-$, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R^8 and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R^5 is selected from the group consisting of -OH, optionally substituted $-OC_1-C_6$ alkyl, $-OC(O)R^e$, $-OC(O)OR^h$, $-NHC(O)OR^h$, $-OC(O)NH(R^h)$, -F, $-NHC(O)R^e$, $-NHS(=O)R^e$, $-NHS(=O)_2R^e$, $-NHC(=S)NH(R^h)$, and $-NHC(O)NH(R^h)$; or

R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^5 are attached, including 0 to 2 heteroatoms independently selected from $-NR^h-$, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is $P(O)(YR^{11})Y''$;

Y'' is selected from the group consisting of hydrogen, optionally substituted $-C_1-C_6$-alkyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2OH$, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-(CR^a_2)_n$cycloalkyl, optionally substituted $(CR^a_2)_n$heterocycloalkyl, $-(CR^a_2)_kS(=O)R^e$, $-(CR^a_2)_kS(=O)_2R^e$, $-(CR^a_2)_kS(=O)_2NR^fR^g$, $-(CR^a_2)_kC(O)NR^fR^g$, and $-(CR^a_2)_kC(O)R^e$;

Y is selected from the group consisting of -O-, and $-NR^y$-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z_2$, $-NR^z$-C(O)-R^y, $-C(R^z)_2$-OC(O)R^y, $-C(R^z)_2$-O-C(O)OR^y, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^y$-, then R^{11} attached to $-NR^y$- is selected from the group consisting of -H, $-[C(R^z)_2]_q$-C(O)OR^y, $-C(R^x)_2C(O)OR^y$, $-[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

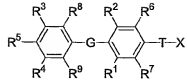
Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cycloalkyl group;

Each R^y is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0265] In another aspect, the invention relates to a compound of Formula VIII:



wherein:

G, T, k, m, n, p, R^a, R^b, R^c, R^1, R^2, R^6, R^7, R^8, R^9, R^i, R^3, R^4, R^d, R^e, R^f, R^g, R^h, R^5, X, Y'', q, R^z, R^y, R^x, and R^v are as defined above;

Y is selected from the group consisting of -O-, and $-NR^v-$;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z_2$, $-NR^z-C(O)-R^y$, $-C(R^z)_2-OC(O)R^y$, $-C(R^z)_2-O-C(O)OR^y$, $-C(R^5)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

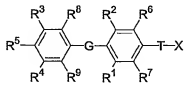
when Y is $-NR^v-$, then R^{11} attached to $-NR^v-$ is selected from the group consisting of -H, $-[C(R^z)_2]_q-C(O)OR^y$, $-C(R^x)_2C(O)OR^y$, $-[C(R^z)_2]_q-C(O)SR^y$, and -cycloalkylene-$C(O)OR^y$;

with the proviso that:

a) when G is -O-, T is $-CH_2-$, R^1 and R^2 are each chloro, R^3 is phenyl, R^4 is hydrogen, and R^5 is –OH, then X is not $P(O)(OH)CH_3$ or $P(O)(OCH_2CH_3)CH_3$;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0266] In a further aspect, the invention relates to a compound of Formula VIII:



wherein:

G, T, k, m, n, p, R^a, R^b, R^c, R^l, R^2, R^6, R^7, R^8, R^9, R^i, R^3, R^4, R^d, R^e, R^f, R^g, R^h, R^5, X, Y'', Y, q, R^z, R^y, R^x, and R^v are as defined above;

Y is selected from the group consisting of -O-, and $-NR^v-$;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z_2$, $-NR^z-C(O)-R^y$, $-C(R^z)_2-OC(O)R^y$, $-C(R^z)_2-O-C(O)OR^y$, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^v-$, then R^{11} attached to $-NR^v-$ is selected from the group consisting of -H, $-[C(R^z)_2]_q-C(O)OR^y$, $-C(R^x)_2C(O)OR^y$, $-[C(R^z)_2]_q-C(O)SR^y$, and -cycloalkylene-$C(O)OR^y$;

with the proviso that:

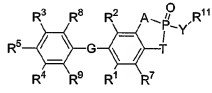
a) when G is -O-, -S-, -Se-, $-S(=O)-$, $-S(=O)_2-$, $-CH_2-$, -C(O)-, -NH- and, T is $-(CH_2)_{0-4}-$ or $-C(O)NH(CR^b_2)-$, R^1 and R^2 are independently chosen from the group consisting of hydrogen, halogen, $-C_1-C_4$ alkyl, R^8 and R^9 are each independently selected from hydrogen, halogen and C_{1-4}alkyl, R^6 and R^7 are each independently selected from hydrogen, halogen O-C_{1-3}alkyl, hydroxy, cyano and C_{1-4}alkyl, R^3 is $-C(O)NR^{25}R^{26}$, $-CH_2-NR^{25}R^{26}$, $-NR^{25}-C(O)R^{26}$, $-OR^{27}$, R^{28}, or  , R^4 is hydrogen, halogen, cyano or alkyl, and R^5 is -OH, R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, cycloalkyl, aralkyl or heteroaralkyl, R^{27} is aryl, heteroaryl, alkyl, aralkyl, or heteroaralkyl, R^{28} is aryl, heteroaryl, or cycloalkyl, R^{29} is hydrogen, aryl, heteroaryl, alkyl, aralkyl, heteroaralkyl, then X is not $-P(O)(OH)C_1-C_6$ alkyl or $-P(O)$(O-lower alkyl)C_1-C_6 alkyl;

b) when G is -O-, -S-, -Se-, $-S(=O)-$, $-S(=O)_2-$, $-CH_2-$, $-CF_2-$, -C(O)-, -NH- and, T is $-C(O)NH(CR^b_2)-$, R^1 and R^2 are independently halogen, cyano, $-C_1-C_4$ alkyl, R^8 and R^9 are each independently selected from hydrogen, halogen and C_{1-4}alkyl, R^6 and R^7 are each independently selected

from hydrogen, halogen O-C_{1-3}alkyl, hydroxy, cyano and C_{1-4}alkyl, R^3 is halogen, -C_1-C_6 alkyl, -C_2-C_6 alkynyl, -C_4-C_7 cycloalkenyl, -C_3-C_7 cycloalkoxy, -$S(=O)_2(NR^{14}R^{15})$, -$N(R^{16})S(=O)_2R^{17}$, -SR^{17}, -$S(=O)R^{17}$, -$S(=O)_2R^{17}$, -$C(O)R^{16}$, or -$CR^{18}(OR^{16})R^{19}$, R^4 is halogen, cyano or alkyl, and R^5 is -OH, optionally substituted -OC_1-C_6 alkyl, aroyl or alkanoyl, R^{14}, R^{15}, R^{16}, R^{18} and R^{19} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, or R^{14} and R^{15} may be joined so as to comprise a chain of 3 to 6 methylene groups to form a ring of 4 to 7-membered in size, R^{17} is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, then X is not –P(O)(OH)C_1-C_6 alkyl or –P(O)(O-lower alkyl)C_1-C_6 alkyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

In one aspect, the invention relates to a compound of Formula XVI:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -$S(=O)_2$-, -Se-,-CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -$CH(C_1$-C_4 alkyl)-, -$CH(C_1$-C_4 alkoxy)-, -$C(=CH_2)$-,-NH-, and -$N(C_1$-C_4 alkyl)-, or CH_2 linked to any of the preceding groups;

or G is R^{50}-R^{51} wherein;

R^{50}-R^{51} together are –$C(R^{52})$=$C(R^{52})$- or alternatively R^{50} and R^{51} are independently selected from O, S and –$CH(R^{53})$-, with the provisos that at least one R^{50} and R^{51} is –$CH(R^{53})$-, and when one of R^{50} and R^{51} is O or S, then R^{53} is R^{54};

R^{54} is hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R^{52} is selected from hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

A and T are each independently selected from the group consisting of $-(CR^a_2)-$, $-(CR^a_2)_2-$, $-O(CR^b_2)-$, $-S(CR^b_2)-$, $-N(R^c)(CR^b_2)-$, $-N(R^b)C(O)-$, $-C(O)(CR^a_2)-$, $-(CR^a_2)C(O)-$, $-(CR^a_2)C(O)-$, $-(CR^b_2)O-$, $-(CR^b_2)S-$, and $-(CR^b_2)N(R^c)-$;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted $-C_1$-C_4 alkyl, halogen, -OH, optionally substituted $-O-C_1$-C_4 alkyl, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-S-C_1$-C_4 alkyl, $-NR^bR^c$, optionally substituted $-C_2$-C_4 alkenyl, and optionally substituted $-C_2$-C_4 alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^b is independently selected from the group consisting of hydrogen and optionally substituted $-C_1$-C_4 alkyl;

Each R^c is independently selected from the group consisting of hydrogen and optionally substituted $-C_1$-C_4 alkyl, optionally substituted $-C(O)-C_1$-C_4 alkyl, and -C(O)H;

R^1, R^2, and R^7 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted $-C_1$-C_4 alkyl, optionally substituted $-S-C_1$-C_3 alkyl, optionally substituted $-C_2$-C_4 alkenyl, optionally substituted $-C_2$-C_4 alkynyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, optionally substituted $-O-C_1$-C_3 alkyl, and cyano; with the proviso that at least one of R^1 and R^2 is not hydrogen;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, optionally substituted -O-C_1-C_3 alkyl, hydroxy, -(CR^a_2)aryl, -(CR^a_2)cycloalkyl, -(CR^a_2)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, cyano, optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -(CR^a_2)$_m$aryl, optionally substituted -(CR^a_2)$_m$cycloalkyl, optionally substituted -(CR^a_2)$_m$heterocycloalkyl, -C(R^b)=C(R^b)-aryl, -C(R^b)=C(R^b)-cycloalkyl, -C(R^b)=C(R^b)-heterocycloalkyl, -C≡C(aryl), -C≡C(cycloalkyl), -C≡C(heterocycloalkyl), -(CR^a_2)$_n$(CR^b_2)NR^fR^g, -OR^d, -SR^d, -S(=O)R^e, -S(=O)$_2R^e$, -S(=O)$_2NR^fR^g$, -C(O)NR^fR^g, -C(O)OR^h, -C(O)R^e, -N(R^b)C(O)R^e, -N(R^b)C(O)NR^fR^g, -N(R^b)S(=O)$_2R^e$, -N(R^b)S(=O)$_2NR^fR^g$, and -NR^fR^g;

Each R^d is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -(CR^b_2)$_n$aryl, optionally substituted -(CR^b_2)$_n$cycloalkyl, optionally substituted -(CR^b_2)$_n$heterocycloalkyl, and -C(O)NR^fR^g;

Each R^e is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -(CR^a_2)$_n$aryl, optionally substituted -(CR^a_2)$_n$cycloalkyl, and optionally substituted -(CR^a_2)$_n$heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -(CR^b_2)$_n$aryl, optionally substituted -(CR^b_2)$_n$cycloalkyl, and optionally

substituted -$(CR^b_2)_n$heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O, NR^e, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$;

Each R^h is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally substituted -$(CR^b_2)_n$cycloalkyl, and optionally substituted -$(CR^b_2)_n$heterocycloalkyl; or

R^3 and R^8 are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^8 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R^8 and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R^5 is selected from the group consisting of -OH, optionally substituted -OC_1-C_6 alkyl, -$OC(O)R^e$, -$OC(O)OR^h$, -$NHC(O)OR^h$, -$OC(O)NH(R^h)$, -F, -$NHC(O)R^e$, -$NHS(=O)R^e$, -$NHS(=O)_2R^e$, -$NHC(=S)NH(R^h)$, and -$NHC(O)NH(R^h)$;

R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^5 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both

heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

Y is selected from the group consisting of -O-, and -NR^v-;

when Y is -O-, R^{11} attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -$C(R^z)_2OC(O)NR^z_2$, -NR^z-$C(O)$-R^y, -$C(R^z)_2$-$OC(O)R^y$, -$C(R^z)_2$-O-$C(O)OR^y$, -$C(R^z)_2OC(O)SR^y$, -alkyl-S-$C(O)R^y$, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR^v-, then R^{11} attached to -NR^v- is independently selected from the group consisting of -H, -$[C(R^z)_2]_q$-$C(O)OR^y$, -$C(R^x)_2C(O)OR^y$, -$[C(R^z)_2]_q$-$C(O)SR^y$, and -cycloalkylene-$C(O)OR^y$;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

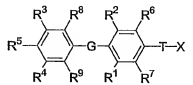
Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cycloalkyl group;

Each R^v is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0267] In one aspect, the invention relates to a compound of Formula XVII:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)$_2$-, -Se-, -CH_2-, -CF_2-, -CHF-, -C(O)-, -CH(OH)-, -CH(C_1-C_4 alkyl)-, -CH(C_1-C_4 alkoxy)-, -C(=CH_2)-,-NH-, and -N(C_1-C_4 alkyl)-, or CH_2 linked to any of the preceding groups;

or G is R^{50}-R^{51} wherein;

R^{50}-R^{51} together are –C(R^{52})=C(R^{52})- or alternatively R^{50} and R^{51} are independently selected from O, S and –CH(R^{53})-, with the provisos that at least one R^{50} and R^{51} is –CH(R^{53})-, and when one of R^{50} and R^{51} is O or S, then R^{53} is R^{54};

R^{54} is hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R^{52} is selected from hydrogen, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of -(CR^a_2)$_n$C(R^b_2)O-, -(CR^a_2)$_n$C(R^b_2)N(R^b)-, -(CR^a_2)$_n$C(R^b_2)S-, -C(O)(CR^a_2)$_p$C(R^b_2)O-, -C(O)(CR^a_2)$_p$C(R^b_2)N(R^b)-, -C(O)(CR^a_2)$_p$C(R^b_2)S-, -(CR^a_2)$_p$C(O)C(R^b_2)O-, -(CR^a_2)$_p$C(O)C(R^b_2)N(R^b)-, and -(CR^a_2)$_p$C(O)C(R^b_2)S-;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each R^a is independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_4 alkyl, halogen, -OH, optionally substituted -O-C_1-C_4 alkyl, -OCF_3, -$OCHF_2$, -OCH_2F, optionally

substituted -S-C_1-C_4 alkyl, -NR^bR^c, optionally substituted -C_2-C_4 alkenyl, and optionally substituted -C_2-C_4 alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

Each R^b is independently selected from the group consisting of hydrogen and optionally substituted -C_1-C_4 alkyl;

Each R^c is independently selected from the group consisting of hydrogen and optionally substituted -C_1-C_4 alkyl, optionally substituted -C(O)-C_1-C_4 alkyl, and -C(O)H;

R^1, R^2, R^6, and R^7 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, optionally substituted -O-C_1-C_3 alkyl, and cyano; with the proviso that at least one of R^1 and R^2 is not hydrogen;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -S-C_1-C_3 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, optionally substituted -O-C_1-C_3 alkyl, hydroxy, -(CR^a_2)aryl, -(CR^a_2)cycloalkyl, -(CR^a_2)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano;

R^i is selected from the group consisting of hydrogen, -C(O)C_1-C_4 alkyl, and -C_1-C_4 alkyl; or

R^1 and R^7 are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^1 and R^7 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, cyano, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^a_2)_m$aryl, optionally substituted $-(CR^a_2)_m$cycloalkyl, optionally substituted $-(CR^a_2)_m$heterocycloalkyl, $-C(R^b)=C(R^b)$-aryl, $-C(R^b)=C(R^b)$-cycloalkyl, $-C(R^b)=C(R^b)$-heterocycloalkyl, $-C\equiv C$(aryl), $-C\equiv C$(cycloalkyl), $-C\equiv C$(heterocycloalkyl), $-(CR^a_2)_n(CR^b_2)NR^fR^g$, $-OR^d$, $-SR^d$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^fR^g$, $-C(O)NR^fR^g$, $-C(O)OR^h$, $-C(O)R^e$, $-N(R^b)C(O)R^e$, $-N(R^b)C(O)NR^fR^g$, $-N(R^b)S(=O)_2R^e$, $-N(R^b)S(=O)_2NR^fR^g$, and $-NR^fR^g$;

Each R^d is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, optionally substituted $-(CR^b_2)_n$heterocycloalkyl, and $-C(O)NR^fR^g$;

Each R^e is selected from the group consisting of optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^a_2)_n$aryl, optionally substituted $-(CR^a_2)_n$cycloalkyl, and optionally substituted $-(CR^a_2)_n$heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_{12}$ alkyl, optionally substituted $-C_2-C_{12}$ alkenyl, optionally substituted $-C_2-C_{12}$ alkynyl, optionally substituted $-(CR^b_2)_n$aryl, optionally substituted $-(CR^b_2)_n$cycloalkyl, and optionally substituted $-(CR^b_2)_n$heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O, NR^e, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally

substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$;

Each R^h is selected from the group consisting of optionally substituted -C_1-C_{12} alkyl, optionally substituted -C_2-C_{12} alkenyl, optionally substituted -C_2-C_{12} alkynyl, optionally substituted -$(CR^b_2)_n$aryl, optionally substituted -$(CR^b_2)_n$cycloalkyl, and optionally substituted -$(CR^b_2)_n$heterocycloalkyl; or

R^3 and R^8 are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^8 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R^9 and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R^5 is selected from the group consisting of -OH, optionally substituted -OC_1-C_6 alkyl, -$OC(O)R^e$, -$OC(O)OR^h$, -$NHC(O)OR^h$, -$OC(O)NH(R^h)$, -F, -$NHC(O)R^e$, -$NHS(=O)R^e$, -$NHS(=O)_2R^e$, -$NHC(=S)NH(R^h)$, and -$NHC(O)NH(R^h)$; or

R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R^3 and R^5 are attached, including 0 to 2 heteroatoms independently selected from –NR^h-, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is $P(O)(YR^{11})Y''$;

Y'' is selected from the group consisting of hydrogen, optionally substituted -C_1-C_6-alkyl, -CF_3, -CHF_2, -CH_2F, -CH_2OH, optionally substituted -C_2-C_6 alkenyl, optionally substituted -C_2-C_6 alkynyl, optionally

substituted -$(CR^a_2)_n$cycloalkyl, optionally substituted $(CR^a_2)_n$heterocycloalkyl, -$(CR^a_2)_kS(=O)R^e$, -$(CR^a_2)_kS(=O)_2R^e$, -$(CR^a_2)_kS(=O)_2NR^fR^g$, -$(CR^a_2)_kC(O)NR^fR^g$, and -$(CR^a_2)_kC(O)R^c$;

Y is selected from the group consisting of -O-, and -NR^v-;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -$C(R^z)_2OC(O)NR^z_2$, -NR^z-C(O)-R^y, -$C(R^z)_2$-OC(O)R^y, -$C(R^z)_2$-O-C(O)OR^y, -$C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR^v-, then R^{11} attached to -NR^v- is selected from the group consisting of -H, -$[C(R^z)_2]_q$-C(O)OR^y, -$C(R^x)_2C(O)OR^y$, -$[C(R^z)_2]_q$-C(O)SR^y, and -cycloalkylene-C(O)OR^y;

q is an integer 2 or 3;

Each R^z is selected from the group consisting of R^y and -H;

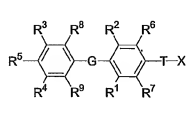
Each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R^x is independently selected from the group consisting of -H, and alkyl, or together R^x and R^x form a cycloalkyl group;

Each R^v is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0268] In another aspect, the invention relates to a compound of Formula XVII:



wherein:

G, T, k, m, n, p, R^a, R^b, R^c, R^1, R^2, R^6, R^7, R^8, R^9, R^i, R^3, R^4, R^d, R^e, R^f, R^g, R^h, R^5, X, Y'', q, R^z, R^y, R^x, and R^v are as defined above;

Y is selected from the group consisting of -O-, and $-NR^v-$;

when Y is -O-, R^{11} attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^5_2$, $-NR^z-C(O)-R^y$, $-C(R^z)_2-OC(O)R^y$, $-C(R^z)_2-O-C(O)OR^y$, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^v-$, then R^{11} attached to $-NR^v-$ is selected from the group consisting of -H, $-[C(R^z)_2]_q-C(O)OR^y$, $-C(R^x)_2C(O)OR^y$, $-[C(R^z)_2]_q-C(O)SR^y$, and -cycloalkylene-C(O)OR^y;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

[0269] For compounds of Formula I, II, III, VIII, XVI, and XVII, in one aspect, G is selected from the group consisting of -O- and $-CH_2-$. In another aspect, G is selected from the group consisting of -O-, -S-, and $-CH_2-$. In a further aspect, G is -O-. In another aspect, G is -S-. In a further aspect, G is -S(=O)-. In another aspect, G is $-S(=O)_2-$. In a further aspect, G is $-CH_2-$. In another aspect, G is $-CF_2-$. In a further aspect, G is -CHF-. In another aspect, G is -C(O)-. In another aspect, G is -CH(OH)-. In a further aspect, G is -NH-. In another aspect, G is $-N(C_1-C_4$ alkyl)-. In yet another aspect, G is –Se-. In another aspect, G is $-CH(C_1-C_4$ alkyl)-. In another aspect, G is $-CH(C_1-C_4$ alkoxy)-. In another aspect, G is $-C(=CH_2)-$. In one aspect G is R^{50}-R^{51} wherein; R^{50}-R^{51} together are $–C(R^{52})=C(R^{52})-$, wherein R^{52} is selected from hydrogen, halogen, mercapto, C_1, C_2, C_3,or C_4 alkyl, C_2, C_3 or C_4 alkenyl, C_2, C_3 or C_4 alkynyl, C_1, C_2, C_3,or C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio. In another aspect one of R^{50} and R^{51} is O and the other is $–CH(R^{54})-$, wherein R^{54} is hydrogen, halogen, C_1, C_2, C_3,or C_4 alkyl, C_2, C_3 or C_4 alkenyl, C_2, C_3 or C_4

alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl. In another aspect one of R^{50} and R^{51} is S and the other is $-CH(R^{54})-$, wherein R^{54} is hydrogen, halogen, C_1, C_2, C_3,or C_4 alkyl, C_2, C_3 or C_4 alkenyl, C_2, C_3 or C_4 alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl. In another aspect both R^{50} and R^{51} are $-CH(R^{53})-$, wherein R^{53} is selected from hydrogen, halogen, hydroxyl, mercapto, C_1, C_2, C_3,or C_4 alkyl, C_2, C_3 or C_4 alkenyl, C_2, C_3 or C_4 alkynyl, C_1, C_2, C_3,or C_4 alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio.

[0270] For compounds of Formula I, III, and VIII, in one aspect, T is $-CH_2-$. In another aspect, T is $-(CH_2)_{0-4}-$. In another aspect, T is selected from the group consisting of $-(CH_2)_{m}-$, $-CH=CH-$, $-O(CH_2)_{1-2}-$, and $-NH(CH_2)_{1-2}-$. In yet another aspect, T is selected from the group consisting of $-(CR^a_2)_n-$, $-O(CR^b_2)(CR^a_2)_p-$, $-N(R^c)(CR^b_2)(CR^a_2)_p-$, $-S(CR^b_2)(CR^a_2)_p-$, $-N(R^b)C(O)-$, and $-CH_2CH(NR^cR^b)-$. In another aspect, T is $-CH_2CH(NH_2)-$. In another aspect, T is $-N(H)C(O)-$. In a further aspect, T is $-OCH_2-$. In another aspect, T is $-CH_2CH_2-$. In yet another aspect, T is $-CH_2CH(NH_2)-$. In another aspect, T is $-N(H)C(O)-$. In a further aspect, T is $-(CR^a_2)_k-$. In another aspect, T is $-CR^b=CR^b-(CR^a_2)_n-$. In a further aspect, T is $-(CR^a_2)_m-CR^b=CR^b-$. In another aspect, T is $-(CR^a_2)-CR^b=CR^b-(CR^a_2)-$. In a further aspect, T is $-O(CR^b_2)(CR^a_2)_n-$ or $-NH(CR^b_2)(CR^a_2)_p-$. In another aspect, T is $-S(CR^b_2)(CR^a_2)_n-$. In a further aspect, T is $-N(R^c)(CR^b_2)(CR^a_2)_n-$. In another aspect, T is $-N(R^b)C(O)(CR^a_2)_n-$. In a further aspect, T is $-(CR^a_2)_nCH(NR^bR^c)-$. In another aspect, T is $-C(O)(CR^a_2)_m-$. In a further aspect, T is $-(CR^a_2)_mC(O)-$. In another aspect, T is $-(CR^a_2)C(O)(CR^a_2)_n-$. In a further aspect, T is $-(CR^a_2)_nC(O)(CR^a_2)-$. In yet another aspect, T is $-C(O)NH(CR^b_2)(CR^a_2)_p-$. In another aspect, T is $-(CR^a_2)_{1-2}-O-(CR^a_2)_{1-2}-$.

[0271] For compounds of Formula II, in a further aspect, D is selected from the group consisting of a bond and $-CH_2-$. In another aspect D is a bond. In a further aspect D is $-(CR^a_2)-$. In another aspect D is $-C(O)-$.

[0272] For compounds of Formula II, in yet another aspect A is selected from -NH-, -NMe-, -O-, and -S-. In one aspect, A is -NR^i-. In another aspect, A is -O-. In a further aspect, A is -S-.

[0273] For compounds of Formula II, in a further aspect, B is selected from -CH_2-, CMe-, and -N-. In another aspect, B is –CR^b-. In a further aspect, B is -N-.

[0274] For compounds of Formula XVI, in another aspect, A and T are each independently selected from the group consisting of -(CR^a_2)-, -$(CR^a_2)_2$-, -$O(CR^b_2)$-, -$S(CR^b_2)$-, -$N(R^c)(CR^b_2)$-, -$N(R^b)C(O)$-, -$C(O)(CR^a_2)$-, -$(CR^a_2)C(O)$-, -$(CR^a_2)C(O)$-, -$(CR^b_2)O$-, -$(CR^b_2)S$-, and -$(CR^b_2)N(R^c)$-.

[0275] For compounds of Formula XVII, in another aspect, T is selected from the group consisting of -$(CR^a_2)_nC(R^b)_2O$-, -$(CR^a_2)_nC(R^b)_2N(R^b)$-, -$(CR^a_2)_nC(R^b)_2S$-, -$C(O)(CR^a_2)_nC(R^b)_2O$-, -$C(O)(CR^a_2)_nC(R^b)_2N(R^b)$-, and -$C(O)(CR^a_2)_nC(R^b)_2S$-. In a further aspect, T is -$(CR^a_2)_nC(R^b)_2O$-, -$(CR^a_2)_nC(R^b)_2N(R^b)$-, -$C(O)(CR^a_2)_pC(R^b)_2O$-, -$C(O)(CR^a_2)_pC(R^b)_2N(R^b)$-, or -$(CR^a_2)_pC(O)C(R^b)_2O$-. In another aspect, T is -$(CR^a_2)_nC(R^b)_2O$-, or -$C(O)(CR^a_2)_pC(R^b)_2O$-. In a further aspect, T is -$(CR^a_2)_nC(R^b)_2O$-. In another aspect, T is -$(CR^a_2)_nC(R^b)_2N(R^b)$-. In a further aspect, T is -$(CR^a_2)_nC(R^b)_2S$-. In another aspect, T is -(-$C(O)(CR^a_2)_nC(R^b)_2O$-. In a further aspect, T is -$C(O)(CR^a_2)_nC(R^b)_2N(R^b)$-. In another aspect, T is -$C(O)(CR^a_2)_nC(R^b)_2S$-.

[0276] For compounds of Formula I, III, VIII, and XVII, in one aspect, k is 0. In a further aspect, k is 1. In an additional aspect, k is 2. In a further aspect, k is 3. In yet another aspect, k is 4. In one aspect, m is 0. In a further aspect, m is 1. In an additional aspect, m is 2. In a further aspect, m is 3. In one aspect, n is 0. In a further aspect, n is 1. In an additional aspect, n is 2. In one aspect, p is 0. In another aspect, p is 1.

[0277] For compounds of Formula I, II, III, VIII, XVI, and XVII, in one aspect, each R^a is hydrogen with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In another aspect, each R^a is

optionally substituted -C_1-C_4 alkyl with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In a further aspect, each R^a is halogen with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In another aspect, each R^a is –OH with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In a further aspect, each R^a is optionally substituted -O-C_1-C_4 alkyl with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In another aspect, each R^a is -OCF_3, $OCHF_2$, or -OCH_2F with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In a further aspect, each R^a is optionally substituted -S-C_1-C_4 alkyl with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In another aspect, each R^a is -NR^bR^c with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In a further aspect, each R^a is optionally substituted -C_2-C_4 alkenyl with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom. In another aspect, each R^a is optionally substituted -C_2-C_4 alkynyl with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom.

[0278] For compounds of Formula I, II, III, VIII, XVI, and XVII, in one aspect, R^b is hydrogen. In an additional aspect, R^b is optionally substituted -C_1-C_4 alkyl.

[0279] For compounds of Formula I, III, VIII, XVI, and XVII, in one aspect, R^c is hydrogen. In another aspect, R^c is optionally substituted -C_1-C_4 alkyl. In

a further aspect, R^c is optionally substituted -C(O)-C_1-C_4 alkyl. In yet another aspect, R^c is -C(O)H.

[0280] For compounds of Formula I, in one aspect, R^1 and R^2 are each bromo. In another aspect, R^1 and R^2 are independently selected from the group consisting of hydrogen, halogen, alkyl of 1 to 3 carbons, and cycloalkyl of 3 to 5 carbons. In another aspect, R^1 and R^2 are independently halogen, alkyl of 1 to 3 carbons, and cycloalkyl of 3 to 5 carbons, In a further aspect, R^1 and R^2 are the same and are selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In an additional aspect, R^1 and R^2 are different and are selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In one aspect, R^1 and R^2 are each independently selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In another aspect, R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano. In another aspect, R^1 and R^2 are each iodo. In one aspect, R^1 and R^2 are both alkyl. In one aspect, R^1 and R^2 are each methyl. In a further aspect, R^1 and R^2 are each chloro. In another aspect, R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, and methyl. In an additional aspect, R^1 and R^2 are each halogen. In another aspect, R^1 and R^2 are not both halogen. In another aspect, R^1 and R^2 are each optionally substituted -C_1-C_4 alkyl. In a further aspect, R^1 and R^2 are each optionally substituted -S-C_1-C_3 alkyl. In another aspect, R^1 and R^2 are each optionally substituted -C_2-C_4 alkenyl. In a further aspect, R^1 and R^2 are each optionally substituted -C_2-C_4 alkynyl. In another aspect, R^1 and R^2 are each -CF_3. In a further aspect, R^1 and R^2 are each -OCF_3, -$OCHF_2$, or -OCH_2F. In another aspect, R^1 and R^2 are each optionally substituted -O-C_1-C_3 alkyl. In a further aspect, R^1 and R^2 are each cyano.

[0281] For compounds of Formula II and III, in one aspect, R^1 and R^2 are the same and are selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In another aspect, R^1 and R^2 are different and are selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In an additional aspect, R^1 and R^2 are

each halogen. In another aspect, R^1 and R^2 are not both halogen. In another aspect, R^1 and R^2 are each optionally substituted -C_1-C_4 alkyl. In a further aspect, R^1 and R^2 are each optionally substituted -S-C_1-C_3 alkyl. In another aspect, R^1 and R^2 are each optionally substituted -C_2-C_4 alkenyl. In a further aspect, R^1 and R^2 are each optionally substituted -C_2-C_4 alkynyl. In another aspect, R^1 and R^2 are each -CF_3, -CHF_2, -CH_2F,. In a further aspect, R^1 and R^2 are each -OCF_3, $OCHF_2$, or -OCH_2F. In another aspect, R^1 and R^2 are each optionally substituted -O-C_1-C_3 alkyl. In a further aspect, R^1 and R^2 are each cyano.

[0282] For compounds of Formula III, in one aspect, R^7 is selected from the group consisting of hydrogen, fluoro, chloro, amino, hydroxy, and -O-CH_3.

[0283] For compounds of Formula VIII, XVI and XVII, in a further aspect, R^1 and R^2 are the same and are selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In yet another aspect, R^1 and R^2 are different and are selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, -CHF_2, -CH_2F, and cyano. In an additional aspect, R^1 and R^2 are each halogen. In an additional aspect, R^1 and R^2 are not both halogen. In another aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each optionally substituted -C_1-C_4 alkyl. In a further aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each optionally substituted -S-C_1-C_3 alkyl. In another aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each optionally substituted -C_2-C_4 alkenyl. In a further aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each optionally substituted -C_2-C_4 alkynyl. In another aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each -CF_3, -CHF_2, or -CH_2F,. In a further aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each -OCF_3, $OCHF_2$, or -OCH_2F. In another aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each optionally substituted-O-C_1-C_3 alkyl. In a further aspect, R^1, R^2, R^6, R^7, R^8, and R^9 are each cyano. In another aspect, R^6 and R^7 are independently selected from the group consisting of hydrogen, halogen, -C_1-C_4 alkyl, cyano, CF_3, -CHF_2, and -CH_2F. In a further aspect, R^6 and R^7 are independently hydrogen, halogen, or methyl. In another aspect, R^8 and R^9 are independently selected from the group consisting of hydrogen, halogen, -C_1-C_4 alkyl, -C_1-C_4 alkylaryl, cyano and CF_3, -CHF_2, and -CH_2F. In a further aspect, R^8 and R^9 are independently

hydrogen, halogen, methyl, benzyl, and benzoate. In another aspect, R^8 and R^9 are each optionally substituted -C_1-C_4 alkylaryl. In another aspect, R^8 and R^9 are each benzyl or benzoate.

[0284] For compounds of Formula VIII, in one aspect, R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms containing 0 to 2 unsaturations and 0 to 2 heteroatoms independently selected from –NR^i-, -O-, and –S- with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring to either a carbon or a nitrogen by either –(CR^a_2)- or -C(O)- or a bond if X is attached directly to a carbon atom. In one aspect, R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms containing 0 unsaturations. In another aspect, R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms containing 1 unsaturation. R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms containing 2 unsaturations. In one aspect, 0 to 2 heteroatoms are -NR^i-. In another aspect, 0 to 2 heteroatoms are –O-. In another aspect, 0 to 2 heteroatoms are –S-.

[0285] For compounds of Formula VIII and XVII, in one aspect, R^1 and R^7 are taken together along with the carbons to which they are attached to form an optionally substituted carbocyclic ring comprising -$(CH_2)_r$-, an optionally substituted ring comprising-CH=CH-CH_2-, an optionally substituted ring comprising-$(CH=CH)_2$-, an optionally substituted ring comprising–(N=CH)-(CH=CH)- or -(CH=N)-(CH=CH)-, or an optionally substituted heterocycle ring comprising-$(CH_2)_t$-Q-$(CH_2)_s$- wherein Q is –O-, -S- or –NR^i-.

[0286] For compounds of Formula VIII, XVI, and XVII, in one aspect, R^3 and R^8 are taken together along with the carbon atoms to which they are attached to form an optionally substituted carbocyclic ring comprising -$(CH_2)_r$-, an optionally substituted ring comprising -CH=CH-CH_2-, an optionally substituted ring comprising -$(CH=CH)_2$-, an optionally substituted ring comprising –(N=CH)-(CH=CH)- or -(CH=N)-(CH=CH)-, or an optionally

substituted heterocycle ring comprising -$(CH_2)_r$-Q-$(CH_2)_s$- wherein Q is –O-, -S- or –NR^i-; or

R^8 and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=.

[0287] For compounds of Formula II, VIII, XVI and XVII, in one aspect, R^i is hydrogen. In another aspect, R^i is -C(O)C_1-C_4 alkyl. In another aspect, R^i is -C_1-C_4 alkyl. In a further aspect, R^i is -C_1-C_4-aryl.

[0288] For compounds of Formula I, II, III, VIII, XVI, and XVII, in yet another aspect, R^3 and R^4 are each hydrogen. In another aspect, R^3 and R^4 are each halogen. In a further aspect, R^3 and R^4 are each -CF_3. In another aspect, R^3 and R^4 are each -OCF_3. In a further aspect, R^3 and R^4 are each cyano. In another aspect, R^3 and R^4 are each optionally substituted -C_1-C_{12} alkyl. In a further aspect, R^3 and R^4 are each optionally substituted -C_2-C_{12} alkenyl. In another aspect, R^3 and R^4 are each optionally substituted -C_2-C_{12} alkynyl. In a further aspect, R^3 and R^4 are each optionally substituted -$(CR^a_2)_m$aryl. In another aspect, R^3 and R^4 are each optionally substituted -$(CR^a_2)_m$cycloalkyl. In a further aspect, R^3 and R^4 are each optionally substituted -$(CR^a_2)_m$heterocycloalkyl. In a further aspect, R^3 and R^4 are each -CH(R^b)=CH(R^b)-aryl. In a further aspect, R^3 and R^4 are each -CH(R^b)=CH(R^b)-cycloalkyl. In a further aspect, R^3 and R^4 are each -CH(R^b)=CH(R^b)-heterocycloalkyl. In a further aspect, R^3 and R^4 are each -C(aryl). In a further aspect, R^3 and R^4 are each -C(cycloalkyl). In a further aspect, R^3 and R^4 are each -C(heterocycloalkyl). In a further aspect, R^3 and R^4 are each -$(CR^a_2)_n(CR^b_2)NR^fR^g$. In another aspect, R^3 and R^4 are each -OR^d. In another aspect, R^3 and R^4 are each -SR^d. In a further aspect, R^3 and R^4 are each -S(=O)R^e. In another aspect, R^3 and R^4 are each -$S(=O)_2R^e$. In a further aspect, R^3 and R^4 are each -$S(=O)_2NR^fR^g$. In another aspect, R^3 and R^4 are each -C(O)NR^fR^g. In a further aspect, R^3 and R^4 are each -C(O)OR^h. In another aspect, R^3 and R^4 are each -C(O)R^e. In a further aspect, R^3 and R^4 are each -N(R^b)C(O)R^e. In another aspect, R^3 and R^4 are each -N(R^b)C(O)NR^fR^g. In a further aspect, R^3 and R^4 are

each $-N(R^b)S(=O)_2R^e$. In another aspect, R^3 and R^4 are each $-N(R^b)S(=O)_2NR^fR^g$. In a further aspect, R^3 and R^4 are each $-NR^fR^g$.

[0289] For compounds of Formula I, in one aspect, R^4 is selected from the group consisting of hydrogen, halogen, $-C_1-C_4$ alkyl, cyano and CF_3. In another aspect, R^4 is not hydrogen. In a further aspect, R^4 is selected from the group consisting of hydrogen and halogen. In another aspect, R^4 is selected from the group consisting of hydrogen and iodo. In a further aspect, R^4 is hydrogen.

[0290] For compounds of Formula II, III, XVI and XVII, in another aspect, R^4 is selected from the group consisting of hydrogen, halogen, $-C_1-C_4$ alkyl, cyano and CF_3. In another aspect, R^4 is hydrogen. In a further aspect, R^3 is selected from the group consisting of halogen, optionally substituted $-C_1-C_6$ alkyl, $-CF_3$, cyano, $-C(O)NR^fR^g$, optionally substituted $-(CR^a_2)_n$aryl, $-SO_2NR^fR^g$, and $-SO_2R^e$. In a further aspect, R^3 is isopropyl or 4-fluorobenzyl.

[0291] For compounds of Formula I, II, III, VIII, XVI, and XVII, in another aspect, each R^d is optionally substituted $-C_1-C_{12}$ alkyl. In a further aspect, each R^d is optionally substituted $-C_2-C_{12}$ alkenyl. In another aspect, each R^d is optionally substituted $-C_2-C_{12}$ alkynyl. In a further aspect, each R^d is optionally substituted $-(CR^b_2)_n$aryl. In another aspect, each R^d is optionally substituted $-(CR^b_2)_n$cycloalkyl. In a further aspect, each R^d is optionally substituted $-(CR^b_2)_n$heterocycloalkyl. In another aspect, each R^d is $-C(O)NR^fR^g$.

[0292] For compounds of Formula I, II, III, VIII, XVI, and XVII, in an additional aspect, R^e is optionally substituted $-C_1-C_{12}$ alkyl. In another aspect, R^e is optionally substituted $-C_2-C_{12}$ alkenyl. In a further aspect, R^e is optionally substituted $-C_2-C_{12}$ alkynyl. In another aspect, R^e is optionally substituted $-(CR^a_2)_n$aryl. In a further aspect, R^e is optionally substituted $-(CR^a_2)_n$cycloalkyl. In another aspect, R^e is optionally substituted $-(CR^a_2)_n$heterocycloalkyl.

[0293] For compounds of Formula I, II, III, VIII, XVI, and XVII, in one aspect, R^f and R^g are each hydrogen. In an additional aspect, R^f and R^g are

each optionally substituted -C_1-C_{12} alkyl. In another aspect, R^f and R^g are each optionally substituted -C_2-C_{12} alkenyl. In an additional aspect, R^f and R^g are each optionally substituted -C_2-C_{12} alkynyl. In a further aspect, R^f and R^g are each optionally substituted -$(CR^b_2)_n$aryl. In an additional aspect, R^f and R^g are each optionally substituted -$(CR^b_2)_n$cycloalkyl. In another aspect, R^f and R^g are each optionally substituted -$(CR^b_2)_n$heterocycloalkyl.

[0294] For compounds of Formula I, II, III, VIII, XVI, and XVII, in an additional aspect, R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup which is O. In another aspect, R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup which is NR^c. In another aspect, R^f and R^g may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup which is S. In one aspect, R^f and R^g may together form an unsubstituted heterocyclic ring, which may contain a second heterogroup. In another aspect, the optionally substituted heterocyclic ring may be substituted with 1 substituent selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$. In further aspect, the optionally substituted heterocyclic ring may be substituted with 2 substituents selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$. In another aspect, the optionally substituted heterocyclic ring may be substituted with 3 substituents selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$. In a further aspect, the optionally substituted heterocyclic ring may be substituted with 4 substituents selected from the group consisting of optionally substituted -C_1-C_4 alkyl, -OR^b, oxo, cyano, -CF_3, -CHF_2, -CH_2F, optionally substituted phenyl, and -$C(O)OR^h$.

[0295] For compounds of Formula I, II, III, VIII, XVI, and XVII, in a further aspect, R^h is optionally substituted -C_1-C_{12} alkyl. In another aspect, R^h is optionally substituted -C_2-C_{12} alkenyl. In a further aspect, R^h is optionally

substituted -C_2-C_{12} alkynyl. In another aspect, R^h is optionally substituted -$(CR^b_2)_n$aryl. In a further aspect, R^h is optionally substituted -$(CR^b_2)_n$cycloalkyl. In another aspect, R^h is optionally substituted -$(CR^b_2)_n$heterocycloalkyl.

[0296] For compounds of Formula I, II, III, VIII, XVI, and XVII, in one aspect, R^5 is selected from the group consisting of -OH, -OC(O)R^e, -OC(O)OR^h, -F, and -NHC(O)R^e. In another aspect, R^5 is -OH. In an additional aspect, R^5 is optionally substituted -OC_1-C_6 alkyl. In another aspect, R^5 is -OC(O)R^e. In a further aspect, R^5 is -OC(O)OR^h. In another aspect, R^5 is -NHC(O)OR^h. In another aspect, R^5 is -OC(O)NH(R^h). In another aspect, R^5 is –F. In another aspect, R^5 is -NHC(O)R^e. In a further aspect, R^5 is -NHS(=O)R^e. In another aspect, R^5 is -NHS(=O)$_2R^e$. In a further aspect, R^5 is -NHC(=S)NH(R^h). In another aspect, R^5 is -NHC(O)NH(R^h).

[0297] For compounds of Formula I, in one aspect, R^3 is selected from the group consisting of halogen, optionally substituted -C_1-C_6 alkyl, -CF_3, cyano, -C(O)NR^fR^g, optionally substituted -$(CR^a2)_n$aryl, -$SO_2NR^fR^g$, and -SO_2R^e. In another aspect, R^3 is *iso*-propyl. In a further aspect, R^3 is alkyl of 1 to 4 carbons or cycloalkyl of 3 to 7 carbons. In yet another aspect, R^3 is selected from the group consisting of halogen, optionally substituted -C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, -S(=O)$_2$-amino, wherein the amino group is seleeted from the group consisting of phenethylamino, piperidinyl, 4-methylpiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R^e wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl. In another aspect, R^3 is iodo. In yet another aspect, R^3 is selected from the group consisting of iodo, bromo, optionally substituted -C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, -S(=O)$_2$-amino, wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R^e wherein R^e is selected from the group consisting of phenyl,

4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl. In one aspect, R^3 is -CH(OH)(4-fluorophenyl). In one aspect, R^3 is isopropyl or 4-fluorobenzyl.

[0298] For compounds of Formula VIII, XVI and XVII, in another aspect, R^3 and R^5 are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations including 0 to 2 heteroatoms independently selected from $-NR^h-$, -O-, and –S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom.

[0299] For compounds of Formula I, II, III, VIII, and XVII, in one aspect, X is $-P(O)YR^{11}Y''$.

[0300] For compounds of Formula I, II, III, VIII, and XVII, in one aspect, Y'' is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, and hexyl. In another aspect, Y'' is methyl. In a further aspect, Y'' is ethyl.

[0301] For compounds of Formula I, II, III, VIII, XVI, and XVII, in one aspect, X is selected from the group consisting of $-P(O)[-OCR^z{}_2OC(O)R^y](Y'')$, $-P(O)[-OCR^z{}_2OC(O)OR^y](Y'')$, and $-P(O)[-N(H)CR^z{}_2C(O)OR^y](Y'')$. In another aspect, is selected from the group consisting of $-P(O)(OH)(Y'')$, $-P(O)(OR^y)(Y'')$, $-P(O)[-OCR^z{}_2OC(O)R^y](Y'')$, $-P(O)[-OCR^z{}_2OC(O)OR^y](Y'')$, and $-P(O)[-N(H)CR^z{}_2C(O)OR^y](Y'')$. In another aspect, X is selected from the group consisting of $-P(O)(OH)(CH_3)$, $-P(O)(OH)(CH_2CH_3)$, $-P(O)[-OCH_2OC(O)$-*t*-butyl$](CH_3)$, $-P(O)[-OCH_2OC(O)O$-*i*-propyl$](CH_3)$, $P(O)[-OCH(CH_3)OC(O)$-*t*-butyl$](CH_3)$, $-P(O)[-OCH(CH_3)OC(O)O$-*i*-propyl$](CH_3)$, $-P(O)[-N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$, and $-P(O)[-N(H)C(CH_3)_2C(O)OCH_2CH_3](CH_3)$. In a further aspect, X is PO_2H_2.

[0302] For compounds of Formula XVI, in one aspect, Y is selected from the group consisting of -O-, and $-NR^y-$.

[0303] For compounds of Formula XVI, in one aspect, when Y is -O-, R^{11} attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl,

optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, $-C(R^z)_2OC(O)NR^z{}_2$, $-NR^z-C(O)-R^y$, $-C(R^z)_2-OC(O)R^y$, $-C(R^z)_2-O-C(O)OR^y$, $-C(R^z)_2OC(O)SR^y$, -alkyl-S-C(O)R^y, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy.

[0304] For compounds of Formula XVI, in a further aspect, when Y is $-NR^v-$, then R^{11} attached to $-NR^v-$ is independently selected from the group consisting of -H, $-[C(R^z)_2]_q-COOR^y$, $-C(R^x)_2COOR^y$, $-[C(R^z)_2]_q-C(O)SR^y$, and -cycloalkylene-$COOR^y$.

[0305] For compounds of Formula I, in a further aspect when G is -O-, T is $-CH_2-$, R^1 and R^2 are each bromo, R^3 is *iso*-propyl, and R^5 is -OH, then R^4 is not hydrogen. In another aspect, when G is -O-, T is $-(CH_2)_{0-4}-$, R^1 and R^2 are independently selected from the group consisting of halogen, alkyl of 1 to 3 carbons, and cycloalkyl of 3 to 5 carbons, R^3 is alkyl of 1 to 4 carbons or cycloalkyl of 3 to 7 carbons, and R^5 is -OH, then R^4 is not hydrogen; and wherein when G is -O-, R^5 is selected from the group consisting of $NHC(O)R^e$, $-NHS(=O)_{1-2}R^e$, $-NHC(=S)NH(R^h)$, and $-NHC(O)NH(R^h)$, T is selected from the group consisting of $-(CH_2)_m-$, -CH=CH-, $-O(CH_2)_{1-2}-$, and $-NH(CH_2)_{1-2}-$, then R^4 is not hydrogen. In a further aspect for the compounds of Formula I, G is selected from the group consisting of -O- and $-CH_2-$; T is selected from the group consisting of $-(CR^a_2)_n$, $-O(CR^b_2)(CR^a_2)_p-$, $-N(R^c)(CR^b_2)(CR^a_2)_p-$, $-S(CR^b_2)(CR^a_2)_p-$, $-N(R^h)C(O)-$, and $-CH_2CH(NR^cR^h)-$; R^1 and R^2 are each independently selected from the group consisting of halogen, $-C_1-C_4$ alkyl, $-CF_3$, and cyano; R^4 is selected from the group consisting of hydrogen, halogen, $-C_1-C_4$ alkyl, cyano and CF_3; R^5 is selected from the group consisting of -OH, $-OC(O)R^e$, $-OC(O)OR^h$, -F and $-NHC(O)R^e$; R^3 is selected from the group consisting of halogen, optionally substituted $-C_1-C_6$ alkyl, $-CF_3$, cyano, $-C(O)NR^fR^g$, optionally substituted $-(CR^a_2)_naryl$, $-SO_2NR^fR^g$, and $-SO_2R^e$; and X is selected from the group consisting of -P(O)(OH)(Y''), $-P(O)(OR^y)(Y'')$, $-P(O)[-OCR^z_2OC(O)OR^y](Y'')$, $-P(O)[-OCR^z_2OC(O)OR^y](Y'')$, and $-P(O)[-N(H)CR^z_2C(O)OR^y](Y'')$.

[0306] For compounds of Formula I, in another aspect, G is selected from the group consisting of -O- and -CH_2-; T is selected from the group consisting of -$(CR^a_2)_n$, -$O(CR^b_2)(CR^a_2)_p$-, -$N(R^c)(CR^b_2)(CR^a_2)_p$-, -$S(CR^b_2)(CR^a_2)_p$-, -$N(R^b)C(O)$-, and -$CH_2CH(NR^cR^b)$-; R^1 and R^2 are each independently selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, and cyano; R^4 is selected from the group consisting of hydrogen, halogen, -C_1-C_4 alkyl, cyano and CF_3; R^5 is selected from the group consisting of -OH, -$OC(O)R^e$, -$OC(O)OR^h$, -F and -$NHC(O)R^e$; R^3 is selected from the group consisting of halogen, optionally substituted -C_1-C_6 alkyl, -CF_3, cyano, -$C(O)NR^fR^g$, optionally substituted -$(CR^a_2)_n$aryl, -$SO_2NR^fR^g$, and -SO_2R^e; and X is selected from the group consisting of -$P(O)(OH)(Y'')$, -$P(O)(OR^y)(Y'')$, -$P(O)[-OCR^z_2OC(O)R^y](Y'')$, -$P(O)[-OCR^z_2OC(O)OR^y](Y'')$, and -$P(O)[-N(H)CR^z_2C(O)OR^y](Y'')$.

[0307] For compounds of Formula I, in an additional aspect, G is selected from the group consisting of -O- and -CH_2-; T is -$CH_2CH(NH_2)$-; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is hydrogen; R^5 is selected from the group consisting of –OH and -$OC(O)R^e$; R^3 is selected from the group consisting of halogen, optionally substituted -C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, -$S(=O)_2$-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R wherein R is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl, and X is selected from the group consisting of -$P(O)(OH)(Y'')$, -$P(O)(OR^y)(Y'')$, -$P(O)[-OCR^z_2OC(O)R^y](Y'')$, -$P(O)[-OCR^z_2OC(O)OR^y](Y'')$, and -$P(O)[-N(H)CR^z_2C(O)OR^y](Y'')$.

[0308] For compounds of Formula I, in another aspect, when G is -O-, T is -CH_2-, R^1 and R^2 are bromo, R^3 is *iso*-propyl, R^5 is -OH, and X is selected from the group consisting of -$P(O)(OH)(Y'')$, -$P(O)(OR^y)(Y'')$,

-P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y''), then R^4 is not hydrogen.

[0309] For compounds of Formula I, in one aspect G is -O-; T is -$CH_2CH(NH_2)$-; R^1 and R^2 are each iodo; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is -OH; and R^3 is iodo; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y'').

[0310] For compounds of Formula I, in another aspect G is -O-; T is -$CH_2CH(NH_2)$-; R^1 and R^2 are each iodo; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is -OH; R^3 is iodo; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y'').

[0311] For compounds of Formula I, in a further aspect G is selected from the group consisting of -O- and -CH_2-; T is -N(H)C(O)-; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen, iodo, 4-chlorophenyl, and cyclohexyl; R^5 is selected from the group consisting of –OH and -OC(O)R^6; R^3 is selected from the group consisting of hydrogen, iodo, bromo, optionally substituted -C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, -S(=O)$_2$-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R wherein R is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y'').

[0312] For compounds of Formula I, an additional aspect is when G is -O-; T is -N(H)C(O)-; R^1 and R^2 are methyl; R^4 is hydrogen; R^5 is -OH; R^3 is -CH(OH)(4-fluorophenyl); and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-$OCR^z_2OC(O)R^y$](Y''), -P(O)[-$OCR^z_2OC(O)OR^y$](Y''), and -P(O)[-$N(H)CR^z_2C(O)OR^y$](Y'').

[0313] For compounds of Formula I, in a further aspect G is selected from the group consisting of -O- and $-CH_2-$; T is $-OCH_2-$; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen, iodo, 4-chlorophenyl, and cyclohexyl; R^5 is selected from the group consisting of -OH and -OC(O)R^c; R^3 is selected from the group consisting of hydrogen, iodo, bromo, optionally substituted lower alkyl, optionally substituted $-CH_2$aryl, optionally substituted -CH(OH)aryl, -C(O)-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, $-S(=O)_2$-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and $-SO_2R$ wherein R is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-$OCR^z_2OC(O)R^y$](Y''), -P(O)[-$OCR^z_2OC(O)OR^y$](Y''), and -P(O)[-$N(H)CR^z_2C(O)OR^y$](Y'').

[0314] For compounds of Formula I, in another aspect G is $-CH_2-$; T is $-OCH_2-$; R^1 and R^2 are each methyl; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-$OCR^z_2OC(O)R^y$](Y''), -P(O)[-$OCR^z_2OC(O)OR^y$](Y''), and -P(O)[-$N(H)CR^z_2C(O)OR^y$](Y'').

[0315] For compounds of Formula I, in a further aspect, G is selected from the group consisting of -O- and $-CH_2-$; T is $-CH_2-$; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen, iodo,

4-chlorophenyl, and cyclohexyl; R^5 is selected from the group consisting of -OH and -OC(O)R^e; R^3 is selected from the group consisting of hydrogen, iodo, bromo, optionally substituted lower alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, -S(=O)$_2$-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl,and-SO_2R wherein R is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl.; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y'').

[0316] For compounds of Formula I, in additional aspects, when G is -O-, T is -CH_2-, R^1 and R^2 are each bromo, R^3 is *iso*-propyl, R^5 is –OH; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y''), then R^4 is not hydrogen.

[0317] For compounds of Formula I, in another aspect, G is -O-; T is -CH_2-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *i*-propyl; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y'').

[0318] For compounds of Formula I, in additional aspects G is selected from the group consisting of -O- and -CH_2-; T is -CH_2CH_2-; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen, iodo, 4-chlorophenyl, and cyclohexyl; R^5 is selected from the group consisting of -OH and -OC(O)R^e; R^3 is selected from the group consisting of hydrogen, iodo, bromo, optionally substituted lower alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino

wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, $-S(=O)_2$-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and $-SO_2R$ wherein R is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and X is selected from the group consisting of -P(O)(OH)(Y''), $-P(O)(OR^y)(Y'')$, $-P(O)[-OCR^z{}_2OC(O)R^y](Y'')$, $-P(O)[-OCR^z{}_2OC(O)OR^y](Y'')$, and $-P(O)[-N(H)CR^z{}_2C(O)OR^y](Y'')$.

[0319] For compounds of Formula I, in a further aspect, G is -O-; T is $-CH_2CH_2$-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and X is selected from the group consisting of -P(O)(OH)(Y''), $-P(O)(OR^y)(Y'')$, $-P(O)[-OCR^z{}_2OC(O)R^y](Y'')$, $-P(O)[-OCR^z{}_2OC(O)OR^y](Y'')$, and $-P(O)[-N(H)CR^z{}_2C(O)OR^y](Y'')$.

[0320] For compounds of Formula I, in an additional aspect, G is $-CH_2$-; T is $-OCH_2$-; R^1 and R^2 are each methyl; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and X is selected from the group consisting of $-P(O)(OH)(CH_3)$ and $-P(O)(OH)(CH_2CH_3)$.. In a further aspect, G is $-CH_2$-; T is $-OCH_2$-; R^1 and R^2 are each methyl; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and X is selected from the group consisting of $-P(O)[-OCH_2OC(O)$-*t*-butyl$](CH_3)$ and $-P(O)[-OCH_2OC(O)O$-*i*-propyl$](CH_3)$. In another aspect, G is $-CH_2$-; T is $-OCH_2$-; R^1 and R^2 are each methyl; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and X is selected from the group consisting of $P(O)[-OCH(CH_3)OC(O)$-*t*-butyl$](CH_3)$ and $-P(O)[-OCH(CH_3)OC(O)O$-*i*-propyl$](CH_3)$. In an additional aspect, G is $-CH_2$-; T is $-OCH_2$-; R^1 and R^2 are each methyl; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and X is selected from the group consisting of $-P(O)[-N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$ and $-P(O)[-N(H)C(CH_3)_2C(O)OCH_2CH_3](CH_3)$.

[0321] For compounds of Formula I, in another aspect, G is -O-, T is $-(CH_2)_{0-4}$-, R^1 and R^2 are independently selected from the group consisting

of hydrogen, halogen, alkyl of 1 to 3 carbons, and cycloalkyl of 3 to 5 carbons, R^3 is alkyl of 1 to 4 carbons or cycloalkyl of 3 to 7 carbons, and R^5 is -OH, then R^4 is not hydrogen; and wherein when G is -O-, R^5 is selected from the group consisting of $NHC(O)R^e$, $-NHS(=O)_{1-2}R^e$, $-NHC(S)NH(R^h)$, and $-NHC(O)NH(R^h)$, T is selected from the group consisting of $-(CH_2)_m-$, -CH=CH-, $-O(CH_2)_{1-2}-$, and $-NH(CH_2)_{1-2}-$, then R^4 is not hydrogen.

[0322] For compounds of Formula I, in another aspect, each R^a is independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_2$ alkyl, halogen, -OH, optionally substituted $-O-C_1-C_2$ alkyl, $-OCF_3$, optionally substituted $-S-C_1-C_2$ alkyl, $-NR^bR^c$, optionally substituted $-C_2$ alkenyl, and optionally substituted $-C_2$ alkynyl;

Each R^b is independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_2$ alkyl;

Each R^c is independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_4$ alkyl, and optionally substituted $-C(O)-C_1-C_2$ alkyl, -C(O)H;

Each R^d is selected from the group consisting of optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-(CR^b_2)_n$phenyl, optionally substituted $-(CR^b_2)_n$monocyclic-heteroaryl, optionally substituted $-(CR^b_2)_n-C_3-C_6$-cycloalkyl, optionally substituted $-(CR^b_2)_n-C_4-C_5$-heterocycloalkyl, and $-C(O)NR^fR^g$;

Each R^e is selected from the group consisting of optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-(CR^b_2)_n$phenyl, optionally substituted $-(CR^b_2)_n$monocyclic-heteroaryl, optionally substituted $-(CR^b_2)_n-C_3-C_6$-cycloalkyl, optionally substituted $-(CR^b_2)_n-C_4-C_5$-heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-(CR^b_2)_n$phenyl, optionally substituted $-(CR^b_2)_n$monocyclic-

heteroaryl, optionally substituted -$(CR^b_2)_n$-C_3-C_6-cycloalkyl, optionally substituted -$(CR^b_2)_n$-C_4-C_5-heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup selected from the group of O, NR^b, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-2 substituents selected from the group consisting of optionally substituted -C_1-C_2 alkyl, -OR^b, oxo, cyano, -CF_3, optionally substituted phenyl, and -$C(O)OR^h$;

Each R^h is optionally substituted -C_1-C_{16} alkyl, optionally substituted -C_2-C_{16} alkenyl, optionally substituted -C_2-C_{16} alkynyl, optionally substituted -$(CR^b_2)_n$phenyl, optionally substituted -$(CR^b_2)_n$monocyclic-heteroaryl, optionally substituted -$(CR^b_2)_n$-C_3-C_6-cycloalkyl, optionally substituted -$(CR^b_2)_n$-C_4-C_5-heterocycloalkyl.

[0323] For compounds of Formula I, in a further aspect, each R^a is independently selected from the group consisting of hydrogen, methyl, fluoro, chloro, -OH, -O-CH_3, -OCF_3, -SCH_3, -$NHCH_3$, -$N(CH_3)_2$;

Each R^b is independently selected from the group consisting of hydrogen, and methyl;

Each R^c is independently selected from the group consisting of hydrogen, methyl, -$C(O)CH_3$, -C(O)H;

Each R^d is selected from the group consisting of optionally substituted -C_1-C_4 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, optionally substituted -$(CH_2)_n$phenyl, optionally substituted -$(CH_2)_n$monocyclic-heteroaryl, optionally substituted -$(CH_2)_n$-C_3-C_6-cycloalkyl, optionally substituted -$(CH_2)_n$-C_4-C_5-heterocycloalkyl, and -$C(O)NR^fR^g$;

Each R^e is selected from the group consisting of optionally substituted -C_1-C_4 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, optionally substituted -$(CH_2)_n$phenyl, optionally substituted -$(CH_2)_n$monocyclic-heteroaryl, optionally substituted -$(CH_2)_n$-C_3-C_6-cycloalkyl, optionally substituted -$(CH_2)_n$-C_4-C_5-heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted -C_1-C_4 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, optionally substituted -$(CH_2)_n$phenyl, optionally substituted -$(CH_2)_n$monocyclic-heteroaryl, optionally substituted -$(CH_2)_n$-C_3-C_6-cycloalkyl, optionally substituted -$(CH_2)_n$-C_4-C_5-heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup selected from the group of O, NR^b, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-2 substituents selected from the group consisting of optionally substituted methyl, -OR^b, oxo, cyano, -CF_3, optionally substituted phenyl, and -$C(O)OR^h$;

Each R^h is optionally substituted -C_1-C_4 alkyl, optionally substituted -C_2-C_4 alkenyl, optionally substituted -C_2-C_4 alkynyl, optionally substituted -$(CH_2)_n$phenyl, optionally substituted -$(CH_2)_n$monocyclic-heteroaryl, optionally substituted -$(CH_2)_n$-C_3-C_6-cycloalkyl, optionally substituted -$(CH_2)_n$-C_4-C_5-heterocycloalkyl.

[0324] For compounds of Formula II, in one aspect, G is selected from the group consisting of -O- and -CH_2-; D is selected from the group consisting of a bond and -CH_2-; A is selected from the group consisting of -NH-, -NMe-, -O-, and -S-; B is selected from the group consisting of –CH-, -CMe-, and -N-; R^1 and R^2 are each independently selected from the group consisting of halogen, -C_1-C_4 alkyl, -CF_3, and cyano; R^4 is selected from the group consisting of hydrogen, halogen, -C_1-C_4 alkyl, cyano and CF_3; R^5 is selected from the group consisting of -OH, -$OC(O)R^e$, -$OC(O)OR^h$, -F, and -$NHC(O)R^e$; R^3 is selected from the group consisting of halogen, optionally substituted -C_1-C_6 alkyl, -CF_3, cyano, -$C(O)NR^fR^g$, optionally substituted -$(CR^a_2)_n$aryl, -$SO_2NR^fR^g$, and -SO_2R^e; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-$OCR^z_2OC(O)R^y$](Y''), -P(O)[-$OCR^z_2OC(O)OR^y$](Y''), and -P(O)[-$N(H)CR^z_2C(O)OR^y$](Y''). In another aspect, G is selected from the group consisting of -O- and -CH_2; D is selected from the group consisting of a bond and -CH_2-; A is selected from the group consisting of -NH-, -NMe-,

-O-, and -S-; B is selected from the group consisting of –CH-, -CMe- and -N-; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen and halogen; R^5 is selected from the group consisting of -OH and $-OC(O)R^e$; and R^3 is selected from the group consisting of halogen, optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-CH_2$aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, $-S(=O)_2$-amino, wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methylpiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and $-SO_2R^e$ wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl. In yet another aspect, G is -O-; D is a bond; A is selected from the group consisting of -NH- and -NMe-; B is selected from the group consisting of –CH- and -CMe-; R^1 and R^2 are each bromo; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is -OH; and R^3 is isopropyl or 4-fluorobenzyl.

[0325] For compounds of Formula II, in another aspect, G is -O-; D is a bond; A is selected from the group consisting of -NH- and -NMe-; B is selected from the group consisting of -CH- and -CMe-; R^1 and R^2 are each bromo; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is -OH; R^3 is isopropyl or 4-fluorobenzyl, and X is selected from the group consisting of $-P(O)(OH)(Y'')$, $-P(O)(OR^y)(Y'')$, $-P(O)[-OCR^z_2OC(O)R^y](Y'')$, $-P(O)[-OCR^z_2OC(O)OR^y](Y'')$, and $-P(O)[-N(H)CR^z_2C(O)OR^y](Y'')$.

[0326] For compounds of Formula III, in one aspect, G is selected from the group consisting of -O- and $-CH_2$-; T is selected from the group consisting of $-(CR^a_2)_{n-}$, $-O(CR^b_2)(CR^a_2)_{p-}$, $-N(R^c)(CR^b_2)(CR^{a2})_{p-}$, $-S(CR^b_2)(CR^a_2)_{p-}$, $-N(R^b)C(O)-$, and $-CH_2CH(NR^cR^b)-$; R^1 and R^2 are each independently selected from the group consisting of halogen, $-C_1-C_4$ alkyl, $-CF_3$, and cyano; R^4 is selected from the group consisting of hydrogen, halogen, $-C_1-C_4$ alkyl, cyano and CF_3; R^5 is selected from the group consisting of -OH, $-OC(O)R^s$, $-OC(O)OR^h$, -F, and $-NHC(O)R^c$; R^3 is selected from the group consisting of halogen, optionally substituted $-C_1-C_6$ alkyl, $-CF_3$, cyano, $-C(O)NR^fR^g$, optionally substituted $-(CR^a_2)_n$aryl, $-SO_2NR^fR^g$,

and $-SO_2R^e$; R^7 is selected from the group consisting of hydrogen, fluoro, chloro, amino, hydroxyl, and $-O-CH_3$; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[$-OCR^z_2OC(O)R^y$](Y''), -P(O)[$-OCR^z_2OC(O)OR^y$](Y''), and -P(O)[$-N(H)CR^z_2C(O)OR^y$](Y'').

[0327] For compounds of Formula III, in a further aspect, when G is -O-, T is $-CH_2-$, R^1 and R^2 are chloro, R^3 is *iso*-propyl, R^7 is fluoro, and R^5 is -OH, then R^4 is not hydrogen. In another aspect, when G is selected from the group consisting of –O- and $-CH_2-$; T is -A-B- where A is selected from the group consisting of $-NR^b-$, -O-, $-CH_2-$ and –S- and B is selected from the group consisting of a bond and substituted or unsubstituted C_1-C_3 alkyl; R^3 is selected from the group consisting of halogen, trifluoromethyl, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryloxy, substituted amide, sulfone, sulfonamide and C_3-C_7 cycloalkyl, wherein said aryl, heteroaryl or cycloalkyl ring(s) are attached or fused to the aromatic; R^4 is selected from the group consisting of hydrogen, halogen, and substituted or unsubstituted C_1-C_4 alkyl; R^1 and R^2 are each independently selected from the group consisting of halogen and substituted or unsubstituted $-C_1$-C_4 alkyl; and R^7 is selected from the group consisting of hydrogen, fluoro, chloro, amino, hydroxyl, and $-O-CH_3$; then R^5 is not hydroxyl, optionally substituted $-OC_1$-C_6 alkyl, or $-OC(O)R^e$.

[0328] For compounds of Formula III, in an additional aspect, T is $-N(H)C(O)-$; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is selected from the group consisting of –OH and $-OC(O)R^e$; R^3 is selected from the group consisting of iodo, bromo, optionally substituted $-C_1$-C_6 alkyl, optionally substituted $-CH_2$aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, $-S(=O)_2$-amino, wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methypiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and $-SO_2R^e$ wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and

4-pyridyl; and R^7 is selected from the group consisting of hydrogen and fluoro.

[0329] For compounds of Formula III, in an additional aspect, T is -N(H)C(O)-; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *-iso*-propyl; and R^7 is fluoro.

[0330] For compounds of Formula III, in an additional aspect, T is -N(H)C(O)-; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is –OH; R^3 is *-iso*-propyl; R^7 is fluoro; X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-$OCR^z_2OC(O)R^y$](Y''), -P(O)[-$OCR^z_2OC(O)OR^y$](Y''), and -P(O)[-$N(H)CR^z_2C(O)OR^y$](Y'').

[0331] For compounds of Formula III, in another aspect, T is -OCH_2-; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is selected from the group consisting of -OH, and -$OC(O)R^e$; R^3 is selected from the group consisting of iodo, bromo, optionally substituted C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, -$S(=O)_2$-amino, wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methylpiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R^e wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and R^7 is selected from the group consisting of hydrogen and fluoro.

[0332] For compounds of Formula III, in another aspect, T is -OCH_2-; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and R^7 is fluoro.

[0333] For compounds of Formula III, in another aspect, T is -OCH_2-; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; R^7 is fluoro; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-$OCR^z_2OC(O)R^y$](Y''), -P(O)[-$OCR^z_2OC(O)OR^y$](Y''), and -P(O)[-$N(H)CR^z_2C(O)OR^y$](Y'').

[0334] For compounds of Formula III, in an additional aspect, T is -CH_2-; R^1 and R^2 are each independently selected from the group consisting of iodo,

bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is selected from the group consisting of -OH, and -OC(O)R^c; R^3 is selected from the group consisting of iodo, bromo, optionally substituted C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, -S(=O)$_2$-amino wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methylpiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R^e wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and R^7 is selected from the group consisting of hydrogen and fluoro.

[0335] For compounds of Formula III, in an additional aspect, T is -CH_2-; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *i*-propyl; and R^7 is fluoro.

[0336] For compounds of Formula III, in an additional aspect, T is -CH_2-; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *i*-propyl; R^7 is fluoro; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[-OCR$^z_2$OC(O)R^y](Y''), -P(O)[-OCR$^z_2$OC(O)OR^y](Y''), and -P(O)[-N(H)CR$^z_2$C(O)OR^y](Y'').

[0337] For compounds of Formula III, in a further aspect, T is -CH_2CH_2-; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is selected from the group consisting of -OH and -OC(O)R^e; R^3 is selected from the group consisting of iodo, bromo, optionally substituted C_1-C_6 alkyl, optionally substituted -CH_2aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, -S(=O)$_2$-amino, wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methylpiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and -SO_2R^e wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and R^7 is selected from the group consisting of hydrogen and fluoro.

[0338] For compounds of Formula III, in another aspect, T is $-CH_2CH_2-$; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; and R^7 is fluoro.

[0339] For compounds of Formula III, in another aspect, T is $-CH_2CH_2-$; G is -O-; R^1 and R^2 are each chloro; R^4 is hydrogen; R^5 is -OH; R^3 is *iso*-propyl; R^7 is fluoro; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[$-OCR^z_2OC(O)R^y$](Y''), -P(O)[$-OCR^z_2OC(O)OR^y$](Y''), and -P(O)[$-N(H)CR^z_2C(O)OR^y$](Y'').

[0340] For compounds of Formula III, in another aspect, T is $-NHCH_2-$; R^1 and R^2 are each independently selected from the group consisting of iodo, bromo, chloro, methyl, and cyano; R^4 is selected from the group consisting of hydrogen and iodo; R^5 is selected from the group consisting of -OH, and $-OC(O)R^e$; R^3 is selected from the group consisting of iodo, bromo, optionally substituted C_1-C_6 alkyl, optionally substituted $-CH_2$aryl, optionally substituted -CH(OH)aryl, -C(O)-amino, $-S(=O)_2$-amino, wherein the amino group is selected from the group consisting of phenethylamino, piperidinyl, 4-methylpiperizinyl, morpholinyl, cyclohexylamino, anilinyl, and indolinyl, and $-SO_2R^e$ wherein R^e is selected from the group consisting of phenyl, 4-chlorophenyl, 4-fluorophenyl, and 4-pyridyl; and R^7 is selected from the group consisting of hydrogen and fluoro.

[0341] For compounds of Formula III, in yet another aspect, T is $-NHCH_2-$; G is –O-; R^1 and R^2 are each chloro; R^4 is selected from the group consisting of hydrogen and iodo R^5 is -OH; R^3 is *iso*-propyl; and R^7 is fluoro.

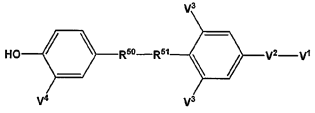
[0342] For compounds of Formula III, in another aspect, T is $-NHCH_2-$; G is -O-; R^1 and R^2 are each bromo; R^4 is selected from the group consisting of hydrogen and iodo R^5 is -OH; R^3 is *iso*-propyl; and R^7 is fluoro.

[0343] For compounds of Formula III, in another aspect, T is $-NHCH_2-$; G is -O-; R^1 and R^2 are each bromo; R^4 is selected from the group consisting of hydrogen and iodo R^5 is -OH; R^3 is *iso*-propyl; R^7 is fluoro; and X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR^y)(Y''), -P(O)[$-OCR^z_2OC(O)R^y$](Y''), -P(O)[$-OCR^z_2OC(O)OR^y$](Y''), and -P(O)[$-N(H)CR^z_2C(O)OR^y$](Y'').

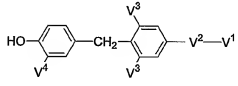
[0344] Each of the individual species of compounds of Formula I, II, III, VIII, XVI, and XVII which can be generated by making all of the above permutations may be specifically set forth as for inclusion or specifically may be excluded from the present invention.

Specific Compounds

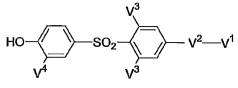
[0345] In one aspect the following compounds are included in the invention but the compounds are not limited to these illustrative compounds. The compounds are shown without depiction of stereochemistry since the compounds are biologically active as the diastereomeric mixture or as a single stereoisomer. Compounds named in Table 2 are designated by numbers assigned to the variables of formulas V-VII using the following convention: $V^1.V^2.V^3.V^4$.



Formula V



Formula VI



Formula VII

[0346] Variable V^1:

1) -P(O)(OH)(CH_3)
2) -P(O)(OH)(CH_2CH_3)
3) -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3)
4) -P(O)[-$OCH_2OC(O)OCH(CH_3)_2$](CH_3)
5) -P(O)[-$OCH(CH_3)OC(O)C(CH_3)_3$](CH_3)
6) -P(O)[-$OCH(CH_3)OC(O)OCH(CH_3)_2$]($CH_3$)
7) -P(O)[-$N(H)CH(CH_3)C(O)OCH_2CH_3$]($CH_3$)
8) -P(O)[-$N(H)C(CH_3)_2C(O)OCH_2CH_3$]($CH_3$)
9) -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_2CH_3)

[0347] Variable V^2:

1) -CH_2-
2) -OCH_2-
3) -CH_2-CH_2-
4) -$NHCH_2$-
5) -NH(CO)-
6) -CH_2-$CH(NH_2)$- (*R*-configuration)
7) -CH_2-$CH(NH_2)$- (*S*-configuration)
8) -CH=CH- (*trans*)
9) - null

[0348] Variable V^3:

1) -Omethyl
2) iodo
3) bromo
4) chloro
5) fluoro
6) methyl
7) trifluoromethyl
8) cyano
9) -OCF_3

[0349] Variable V^4:

1) iodo

2) $CH(CH_3)_2$

3) C_6H_{11}

4) C_6H_5

5) $-C(O)NHC_6H_{11}$

6) -CH(OH)(4-fluorophenyl)

7) $-SO_2$(4-fluorophenyl)

8) $-SO_2$(*N*-piperazinyl)

9) bromo

[0350] In another aspect additional compounds are listed in Table 2 using Formula V, VI or VII. For example, the compound 1.3.6.7 from Formula V represents the compound of Formula V wherein V^1 is 1, *i.e.*, of group V^1 is 1, *i.e.*, of group $-P(O)(OH)_2$; V^2 is 3, *i.e.*, of group $-CH_2-CH_2-$; V^3 is 6, *i.e.*, of group methyl; and V^4 is 7, *i.e.*, of group $-SO_2$(4-fluorophenyl).

Table 2

1.1.1.1	1.1.1.2	1.1.1.3	1.1.1.4	1.1.1.5	1.1.1.6	1.1.1.7	1.1.1.8	1.1.1.9	1.1.2.1
1.1.2.2	1.1.2.3	1.1.2.4	1.1.2.5	1.1.2.6	1.1.2.7	1.1.2.8	1.1.2.9	1.1.3.1	1.1.3.2
1.1.3.3	1.1.3.4	1.1.3.5	1.1.3.6	1.1.3.7	1.1.3.8	1.1.3.9	1.1.4.1	1.1.4.2	1.1.4.3
1.1.4.4	1.1.4.5	1.1.4.6	1.1.4.7	1.1.4.8	1.1.4.9	1.1.5.1	1.1.5.2	1.1.5.3	1.1.5.4
1.1.5.5	1.1.5.6	1.1.5.7	1.1.5.8	1.1.5.9	1.1.6.1	1.1.6.2	1.1.6.3	1.1.6.4	1.1.6.5
1.1.6.6	1.1.6.7	1.1.6.8	1.1.6.9	1.1.7.1	1.1.7.2	1.1.7.3	1.1.7.4	1.1.7.5	1.1.7.6
1.1.7.7	1.1.7.8	1.1.7.9	1.1.8.1	1.1.8.2	1.1.8.3	1.1.8.4	1.1.8.5	1.1.8.6	1.1.8.7
1.1.8.8	1.1.8.9	1.1.9.1	1.1.9.2	1.1.9.3	1.1.9.4	1.1.9.5	1.1.9.6	1.1.9.7	1.1.9.8
1.1.9.9	1.2.1.1	1.2.1.2	1.2.1.3	1.2.1.4	1.2.1.5	1.2.1.6	1.2.1.7	1.2.1.8	1.2.1.9
1.2.2.1	1.2.2.2	1.2.2.3	1.2.2.4	1.2.2.5	1.2.2.6	1.2.2.7	1.2.2.8	1.2.2.9	1.2.3.1
1.2.3.2	1.2.3.3	1.2.3.4	1.2.3.5	1.2.3.6	1.2.3.7	1.2.3.8	1.2.3.9	1.2.4.1	1.2.4.2
1.2.4.3	1.2.4.4	1.2.4.5	1.2.4.6	1.2.4.7	1.2.4.8	1.2.4.9	1.2.5.1	1.2.5.2	1.2.5.3
1.2.5.4	1.2.5.5	1.2.5.6	1.2.5.7	1.2.5.8	1.2.5.9	1.2.6.1	1.2.6.2	1.2.6.3	1.2.6.4
1.2.6.5	1.2.6.6	1.2.6.7	1.2.6.8	1.2.6.9	1.2.7.1	1.2.7.2	1.2.7.3	1.2.7.4	1.2.7.5
1.2.7.6	1.2.7.7	1.2.7.8	1.2.7.9	1.2.8.1	1.2.8.2	1.2.8.3	1.2.8.4	1.2.8.5	1.2.8.6
1.2.8.7	1.2.8.8	1.2.8.9	1.2.9.1	1.2.9.2	1.2.9.3	1.2.9.4	1.2.9.5	1.2.9.6	1.2.9.7
1.2.9.8	1.2.9.9	1.3.1.1	1.3.1.2	1.3.1.3	1.3.1.4	1.3.1.5	1.3.1.6	1.3.1.7	1.3.1.8
1.3.1.9	1.3.2.1	1.3.2.2	1.3.2.3	1.3.2.4	1.3.2.5	1.3.2.6	1.3.2.7	1.3.2.8	1.3.2.9
1.3.3.1	1.3.3.2	1.3.3.3	1.3.3.4	1.3.3.5	1.3.3.6	1.3.3.7	1.3.3.8	1.3.3.9	1.3.4.1
1.3.4.2	1.3.4.3	1.3.4.4	1.3.4.5	1.3.4.6	1.3.4.7	1.3.4.8	1.3.4.9	1.3.5.1	1.3.5.2
1.3.5.3	1.3.5.4	1.3.5.5	1.3.5.6	1.3.5.7	1.3.5.8	1.3.5.9	1.3.6.1	1.3.6.2	1.3.6.3
1.3.6.4	1.3.6.5	1.3.6.6	1.3.6.7	1.3.6.8	1.3.6.9	1.3.7.1	1.3.7.2	1.3.7.3	1.3.7.4
1.3.7.5	1.3.7.6	1.3.7.7	1.3.7.8	1.3.7.9	1.3.8.1	1.3.8.2	1.3.8.3	1.3.8.4	1.3.8.5
1.3.8.6	1.3.8.7	1.3.8.8	1.3.8.9	1.3.9.1	1.3.9.2	1.3.9.3	1.3.9.4	1.3.9.5	1.3.9.6
1.3.9.7	1.3.9.8	1.3.9.9	1.4.1.1	1.4.1.2	1.4.1.3	1.4.1.4	1.4.1.5	1.4.1.6	1.4.1.7
1.4.1.8	1.4.1.9	1.4.2.1	1.4.2.2	1.4.2.3	1.4.2.4	1.4.2.5	1.4.2.6	1.4.2.7	1.4.2.8
1.4.2.9	1.4.3.1	1.4.3.2	1.4.3.3	1.4.3.4	1.4.3.5	1.4.3.6	1.4.3.7	1.4.3.8	1.4.3.9
1.4.4.1	1.4.4.2	1.4.4.3	1.4.4.4	1.4.4.5	1.4.4.6	1.4.4.7	1.4.4.8	1.4.4.9	1.4.5.1
1.4.5.2	1.4.5.3	1.4.5.4	1.4.5.5	1.4.5.6	1.4.5.7	1.4.5.8	1.4.5.9	1.4.6.1	1.4.6.2
1.4.6.3	1.4.6.4	1.4.6.5	1.4.6.6	1.4.6.7	1.4.6.8	1.4.6.9	1.4.7.1	1.4.7.2	1.4.7.3
1.4.7.4	1.4.7.5	1.4.7.6	1.4.7.7	1.4.7.8	1.4.7.9	1.4.8.1	1.4.8.2	1.4.8.3	1.4.8.4
1.4.8.5	1.4.8.6	1.4.8.7	1.4.8.8	1.4.8.9	1.4.9.1	1.4.9.2	1.4.9.3	1.4.9.4	1.4.9.5
1.4.9.6	1.4.9.7	1.4.9.8	1.4.9.9	1.5.1.1	1.5.1.2	1.5.1.3	1.5.1.4	1.5.1.5	1.5.1.6
1.5.1.7	1.5.1.8	1.5.1.9	1.5.2.1	1.5.2.2	1.5.2.3	1.5.2.4	1.5.2.5	1.5.2.6	1.5.2.7
1.5.2.8	1.5.2.9	1.5.3.1	1.5.3.2	1.5.3.3	1.5.3.4	1.5.3.5	1.5.3.6	1.5.3.7	1.5.3.8
1.5.3.9	1.5.4.1	1.5.4.2	1.5.4.3	1.5.4.4	1.5.4.5	1.5.4.6	1.5.4.7	1.5.4.8	1.5.4.9
1.5.5.1	1.5.5.2	1.5.5.3	1.5.5.4	1.5.5.5	1.5.5.6	1.5.5.7	1.5.5.8	1.5.5.9	1.5.6.1
1.5.6.2	1.5.6.3	1.5.6.4	1.5.6.5	1.5.6.6	1.5.6.7	1.5.6.8	1.5.6.9	1.5.7.1	1.5.7.2
1.5.7.3	1.5.7.4	1.5.7.5	1.5.7.6	1.5.7.7	1.5.7.8	1.5.7.9	1.5.8.1	1.5.8.2	1.5.8.3
1.5.8.4	1.5.8.5	1.5.8.6	1.5.8.7	1.5.8.8	1.5.8.9	1.5.9.1	1.5.9.2	1.5.9.3	1.5.9.4
1.5.9.5	1.5.9.6	1.5.9.7	1.5.9.8	1.5.9.9	1.6.1.1	1.6.1.2	1.6.1.3	1.6.1.4	1.6.1.5
1.6.1.6	1.6.1.7	1.6.1.8	1.6.1.9	1.6.2.1	1.6.2.2	1.6.2.3	1.6.2.4	1.6.2.5	1.6.2.6
1.6.2.7	1.6.2.8	1.6.2.9	1.6.3.1	1.6.3.2	1.6.3.3	1.6.3.4	1.6.3.5	1.6.3.6	1.6.3.7
1.6.3.8	1.6.3.9	1.6.4.1	1.6.4.2	1.6.4.3	1.6.4.4	1.6.4.5	1.6.4.6	1.6.4.7	1.6.4.8
1.6.4.9	1.6.5.1	1.6.5.2	1.6.5.3	1.6.5.4	1.6.5.5	1.6.5.6	1.6.5.7	1.6.5.8	1.6.5.9
1.6.6.1	1.6.6.2	1.6.6.3	1.6.6.4	1.6.6.5	1.6.6.6	1.6.6.7	1.6.6.8	1.6.6.9	1.6.7.1
1.6.7.2	1.6.7.3	1.6.7.4	1.6.7.5	1.6.7.6	1.6.7.7	1.6.7.8	1.6.7.9	1.6.8.1	1.6.8.2
1.6.8.3	1.6.8.4	1.6.8.5	1.6.8.6	1.6.8.7	1.6.8.8	1.6.8.9	1.6.9.1	1.6.9.2	1.6.9.3

Table 2 - continued

1.6.9.4	1.6.9.5	1.6.9.6	1.6.9.7	1.6.9.8	1.6.9.9	1.7.1.1	1.7.1.2	1.7.1.3	1.7.1.4
1.7.1.5	1.7.1.6	1.7.1.7	1.7.1.8	1.7.1.9	1.7.2.1	1.7.2.2	1.7.2.3	1.7.2.4	1.7.2.5
1.7.2.6	1.7.2.7	1.7.2.8	1.7.2.9	1.7.3.1	1.7.3.2	1.7.3.3	1.7.3.4	1.7.3.5	1.7.3.6
1.7.3.7	1.7.3.8	1.7.3.9	1.7.4.1	1.7.4.2	1.7.4.3	1.7.4.4	1.7.4.5	1.7.4.6	1.7.4.7
1.7.4.8	1.7.4.9	1.7.5.1	1.7.5.2	1.7.5.3	1.7.5.4	1.7.5.5	1.7.5.6	1.7.5.7	1.7.5.8
1.7.5.9	1.7.6.1	1.7.6.2	1.7.6.3	1.7.6.4	1.7.6.5	1.7.6.6	1.7.6.7	1.7.6.8	1.7.6.9
1.7.7.1	1.7.7.2	1.7.7.3	1.7.7.4	1.7.7.5	1.7.7.6	1.7.7.7	1.7.7.8	1.7.7.9	1.7.8.1
1.7.8.2	1.7.8.3	1.7.8.4	1.7.8.5	1.7.8.6	1.7.8.7	1.7.8.8	1.7.8.9	1.7.9.1	1.7.9.2
1.7.9.3	1.7.9.4	1.7.9.5	1.7.9.6	1.7.9.7	1.7.9.8	1.7.9.9	1.8.1.1	1.8.1.2	1.8.1.3
1.8.1.4	1.8.1.5	1.8.1.6	1.8.1.7	1.8.1.8	1.8.1.9	1.8.2.1	1.8.2.2	1.8.2.3	1.8.2.4
1.8.2.5	1.8.2.6	1.8.2.7	1.8.2.8	1.8.2.9	1.8.3.1	1.8.3.2	1.8.3.3	1.8.3.4	1.8.3.5
1.8.3.6	1.8.3.7	1.8.3.8	1.8.3.9	1.8.4.1	1.8.4.2	1.8.4.3	1.8.4.4	1.8.4.5	1.8.4.6
1.8.4.7	1.8.4.8	1.8.4.9	1.8.5.1	1.8.5.2	1.8.5.3	1.8.5.4	1.8.5.5	1.8.5.6	1.8.5.7
1.8.5.8	1.8.5.9	1.8.6.1	1.8.6.2	1.8.6.3	1.8.6.4	1.8.6.5	1.8.6.6	1.8.6.7	1.8.6.8
1.8.6.9	1.8.7.1	1.8.7.2	1.8.7.3	1.8.7.4	1.8.7.5	1.8.7.6	1.8.7.7	1.8.7.8	1.8.7.9
1.8.8.1	1.8.8.2	1.8.8.3	1.8.8.4	1.8.8.5	1.8.8.6	1.8.8.7	1.8.8.8	1.8.8.9	1.8.9.1
1.8.9.2	1.8.9.3	1.8.9.4	1.8.9.5	1.8.9.6	1.8.9.7	1.8.9.8	1.8.9.9	1.9.1.1	1.9.1.2
1.9.1.3	1.9.1.4	1.9.1.5	1.9.1.6	1.9.1.7	1.9.1.8	1.9.1.9	1.9.2.1	1.9.2.2	1.9.2.3
1.9.2.4	1.9.2.5	1.9.2.6	1.9.2.7	1.9.2.8	1.9.2.9	1.9.3.1	1.9.3.2	1.9.3.3	1.9.3.4
1.9.3.5	1.9.3.6	1.9.3.7	1.9.3.8	1.9.3.9	1.9.4.1	1.9.4.2	1.9.4.3	1.9.4.4	1.9.4.5
1.9.4.6	1.9.4.7	1.9.4.8	1.9.4.9	1.9.5.1	1.9.5.2	1.9.5.3	1.9.5.4	1.9.5.5	1.9.5.6
1.9.5.7	1.9.5.8	1.9.5.9	1.9.6.1	1.9.6.2	1.9.6.3	1.9.6.4	1.9.6.5	1.9.6.6	1.9.6.7
1.9.6.8	1.9.6.9	1.9.7.1	1.9.7.2	1.9.7.3	1.9.7.4	1.9.7.5	1.9.7.6	1.9.7.7	1.9.7.8
1.9.7.9	1.9.8.1	1.9.8.2	1.9.8.3	1.9.8.4	1.9.8.5	1.9.8.6	1.9.8.7	1.9.8.8	1.9.8.9
1.9.9.1	1.9.9.2	1.9.9.3	1.9.9.4	1.9.9.5	1.9.9.6	1.9.9.7	1.9.9.8	1.9.9.9	2.1.1.1
2.1.1.2	2.1.1.3	2.1.1.4	2.1.1.5	2.1.1.6	2.1.1.7	2.1.1.8	2.1.1.9	2.1.2.1	2.1.2.2
2.1.2.3	2.1.2.4	2.1.2.5	2.1.2.6	2.1.2.7	2.1.2.8	2.1.2.9	2.1.3.1	2.1.3.2	2.1.3.3
2.1.3.4	2.1.3.5	2.1.3.6	2.1.3.7	2.1.3.8	2.1.3.9	2.1.4.1	2.1.4.2	2.1.4.3	2.1.4.4
2.1.4.5	2.1.4.6	2.1.4.7	2.1.4.8	2.1.4.9	2.1.5.1	2.1.5.2	2.1.5.3	2.1.5.4	2.1.5.5
2.1.5.6	2.1.5.7	2.1.5.8	2.1.5.9	2.1.6.1	2.1.6.2	2.1.6.3	2.1.6.4	2.1.6.5	2.1.6.6
2.1.6.7	2.1.6.8	2.1.6.9	2.1.7.1	2.1.7.2	2.1.7.3	2.1.7.4	2.1.7.5	2.1.7.6	2.1.7.7
2.1.7.8	2.1.7.9	2.1.8.1	2.1.8.2	2.1.8.3	2.1.8.4	2.1.8.5	2.1.8.6	2.1.8.7	2.1.8.8
2.1.8.9	2.1.9.1	2.1.9.2	2.1.9.3	2.1.9.4	2.1.9.5	2.1.9.6	2.1.9.7	2.1.9.8	2.1.9.9
2.2.1.1	2.2.1.2	2.2.1.3	2.2.1.4	2.2.1.5	2.2.1.6	2.2.1.7	2.2.1.8	2.2.1.9	2.2.2.1
2.2.2.2	2.2.2.3	2.2.2.4	2.2.2.5	2.2.2.6	2.2.2.7	2.2.2.8	2.2.2.9	2.2.3.1	2.2.3.2
2.2.3.3	2.2.3.4	2.2.3.5	2.2.3.6	2.2.3.7	2.2.3.8	2.2.3.9	2.2.4.1	2.2.4.2	2.2.4.3
2.2.4.4	2.2.4.5	2.2.4.6	2.2.4.7	2.2.4.8	2.2.4.9	2.2.5.1	2.2.5.2	2.2.5.3	2.2.5.4
2.2.5.5	2.2.5.6	2.2.5.7	2.2.5.8	2.2.5.9	2.2.6.1	2.2.6.2	2.2.6.3	2.2.6.4	2.2.6.5
2.2.6.6	2.2.6.7	2.2.6.8	2.2.6.9	2.2.7.1	2.2.7.2	2.2.7.3	2.2.7.4	2.2.7.5	2.2.7.6
2.2.7.7	2.2.7.8	2.2.7.9	2.2.8.1	2.2.8.2	2.2.8.3	2.2.8.4	2.2.8.5	2.2.8.6	2.2.8.7
2.2.8.8	2.2.8.9	2.2.9.1	2.2.9.2	2.2.9.3	2.2.9.4	2.2.9.5	2.2.9.6	2.2.9.7	2.2.9.8
2.2.9.9	2.3.1.1	2.3.1.2	2.3.1.3	2.3.1.4	2.3.1.5	2.3.1.6	2.3.1.7	2.3.1.8	2.3.1.9
2.3.2.1	2.3.2.2	2.3.2.3	2.3.2.4	2.3.2.5	2.3.2.6	2.3.2.7	2.3.2.8	2.3.2.9	2.3.3.1
2.3.3.2	2.3.3.3	2.3.3.4	2.3.3.5	2.3.3.6	2.3.3.7	2.3.3.8	2.3.3.9	2.3.4.1	2.3.4.2
2.3.4.3	2.3.4.4	2.3.4.5	2.3.4.6	2.3.4.7	2.3.4.8	2.3.4.9	2.3.5.1	2.3.5.2	2.3.5.3
2.3.5.4	2.3.5.5	2.3.5.6	2.3.5.7	2.3.5.8	2.3.5.9	2.3.6.1	2.3.6.2	2.3.6.3	2.3.6.4
2.3.6.5	2.3.6.6	2.3.6.7	2.3.6.8	2.3.6.9	2.3.7.1	2.3.7.2	2.3.7.3	2.3.7.4	2.3.7.5
2.3.7.6	2.3.7.7	2.3.7.8	2.3.7.9	2.3.8.1	2.3.8.2	2.3.8.3	2.3.8.4	2.3.8.5	2.3.8.6

Table 2 - continued

2.3.8.7	2.3.8.8	2.3.8.9	2.3.9.1	2.3.9.2	2.3.9.3	2.3.9.4	2.3.9.5	2.3.9.6	2.3.9.7
2.3.9.8	2.3.9.9	2.4.1.1	2.4.1.2	2.4.1.3	2.4.1.4	2.4.1.5	2.4.1.6	2.4.1.7	2.4.1.8
2.4.1.9	2.4.2.1	2.4.2.2	2.4.2.3	2.4.2.4	2.4.2.5	2.4.2.6	2.4.2.7	2.4.2.8	2.4.2.9
2.4.3.1	2.4.3.2	2.4.3.3	2.4.3.4	2.4.3.5	2.4.3.6	2.4.3.7	2.4.3.8	2.4.3.9	2.4.4.1
2.4.4.2	2.4.4.3	2.4.4.4	2.4.4.5	2.4.4.6	2.4.4.7	2.4.4.8	2.4.4.9	2.4.5.1	2.4.5.2
2.4.5.3	2.4.5.4	2.4.5.5	2.4.5.6	2.4.5.7	2.4.5.8	2.4.5.9	2.4.6.1	2.4.6.2	2.4.6.3
2.4.6.4	2.4.6.5	2.4.6.6	2.4.6.7	2.4.6.8	2.4.6.9	2.4.7.1	2.4.7.2	2.4.7.3	2.4.7.4
2.4.7.5	2.4.7.6	2.4.7.7	2.4.7.8	2.4.7.9	2.4.8.1	2.4.8.2	2.4.8.3	2.4.8.4	2.4.8.5
2.4.8.6	2.4.8.7	2.4.8.8	2.4.8.9	2.4.9.1	2.4.9.2	2.4.9.3	2.4.9.4	2.4.9.5	2.4.9.6
2.4.9.7	2.4.9.8	2.4.9.9	2.5.1.1	2.5.1.2	2.5.1.3	2.5.1.4	2.5.1.5	2.5.1.6	2.5.1.7
2.5.1.8	2.5.1.9	2.5.2.1	2.5.2.2	2.5.2.3	2.5.2.4	2.5.2.5	2.5.2.6	2.5.2.7	2.5.2.8
2.5.2.9	2.5.3.1	2.5.3.2	2.5.3.3	2.5.3.4	2.5.3.5	2.5.3.6	2.5.3.7	2.5.3.8	2.5.3.9
2.5.4.1	2.5.4.2	2.5.4.3	2.5.4.4	2.5.4.5	2.5.4.6	2.5.4.7	2.5.4.8	2.5.4.9	2.5.5.1
2.5.5.2	2.5.5.3	2.5.5.4	2.5.5.5	2.5.5.6	2.5.5.7	2.5.5.8	2.5.5.9	2.5.6.1	2.5.6.2
2.5.6.3	2.5.6.4	2.5.6.5	2.5.6.6	2.5.6.7	2.5.6.8	2.5.6.9	2.5.7.1	2.5.7.2	2.5.7.3
2.5.7.4	2.5.7.5	2.5.7.6	2.5.7.7	2.5.7.8	2.5.7.9	2.5.8.1	2.5.8.2	2.5.8.3	2.5.8.4
2.5.8.5	2.5.8.6	2.5.8.7	2.5.8.8	2.5.8.9	2.5.9.1	2.5.9.2	2.5.9.3	2.5.9.4	2.5.9.5
2.5.9.6	2.5.9.7	2.5.9.8	2.5.9.9	2.6.1.1	2.6.1.2	2.6.1.3	2.6.1.4	2.6.1.5	2.6.1.6
2.6.1.7	2.6.1.8	2.6.1.9	2.6.2.1	2.6.2.2	2.6.2.3	2.6.2.4	2.6.2.5	2.6.2.6	2.6.2.7
2.6.2.8	2.6.2.9	2.6.3.1	2.6.3.2	2.6.3.3	2.6.3.4	2.6.3.5	2.6.3.6	2.6.3.7	2.6.3.8
2.6.3.9	2.6.4.1	2.6.4.2	2.6.4.3	2.6.4.4	2.6.4.5	2.6.4.6	2.6.4.7	2.6.4.8	2.6.4.9
2.6.5.1	2.6.5.2	2.6.5.3	2.6.5.4	2.6.5.5	2.6.5.6	2.6.5.7	2.6.5.8	2.6.5.9	2.6.6.1
2.6.6.2	2.6.6.3	2.6.6.4	2.6.6.5	2.6.6.6	2.6.6.7	2.6.6.8	2.6.6.9	2.6.7.1	2.6.7.2
2.6.7.3	2.6.7.4	2.6.7.5	2.6.7.6	2.6.7.7	2.6.7.8	2.6.7.9	2.6.8.1	2.6.8.2	2.6.8.3
2.6.8.4	2.6.8.5	2.6.8.6	2.6.8.7	2.6.8.8	2.6.8.9	2.6.9.1	2.6.9.2	2.6.9.3	2.6.9.4
2.6.9.5	2.6.9.6	2.6.9.7	2.6.9.8	2.6.9.9	2.7.1.1	2.7.1.2	2.7.1.3	2.7.1.4	2.7.1.5
2.7.1.6	2.7.1.7	2.7.1.8	2.7.1.9	2.7.2.1	2.7.2.2	2.7.2.3	2.7.2.4	2.7.2.5	2.7.2.6
2.7.2.7	2.7.2.8	2.7.2.9	2.7.3.1	2.7.3.2	2.7.3.3	2.7.3.4	2.7.3.5	2.7.3.6	2.7.3.7
2.7.3.8	2.7.3.9	2.7.4.1	2.7.4.2	2.7.4.3	2.7.4.4	2.7.4.5	2.7.4.6	2.7.4.7	2.7.4.8
2.7.4.9	2.7.5.1	2.7.5.2	2.7.5.3	2.7.5.4	2.7.5.5	2.7.5.6	2.7.5.7	2.7.5.8	2.7.5.9
2.7.6.1	2.7.6.2	2.7.6.3	2.7.6.4	2.7.6.5	2.7.6.6	2.7.6.7	2.7.6.8	2.7.6.9	2.7.7.1
2.7.7.2	2.7.7.3	2.7.7.4	2.7.7.5	2.7.7.6	2.7.7.7	2.7.7.8	2.7.7.9	2.7.8.1	2.7.8.2
2.7.8.3	2.7.8.4	2.7.8.5	2.7.8.6	2.7.8.7	2.7.8.8	2.7.8.9	2.7.9.1	2.7.9.2	2.7.9.3
2.7.9.4	2.7.9.5	2.7.9.6	2.7.9.7	2.7.9.8	2.7.9.9	2.8.1.1	2.8.1.2	2.8.1.3	2.8.1.4
2.8.1.5	2.8.1.6	2.8.1.7	2.8.1.8	2.8.1.9	2.8.2.1	2.8.2.2	2.8.2.3	2.8.2.4	2.8.2.5
2.8.2.6	2.8.2.7	2.8.2.8	2.8.2.9	2.8.3.1	2.8.3.2	2.8.3.3	2.8.3.4	2.8.3.5	2.8.3.6
2.8.3.7	2.8.3.8	2.8.3.9	2.8.4.1	2.8.4.2	2.8.4.3	2.8.4.4	2.8.4.5	2.8.4.6	2.8.4.7
2.8.4.8	2.8.4.9	2.8.5.1	2.8.5.2	2.8.5.3	2.8.5.4	2.8.5.5	2.8.5.6	2.8.5.7	2.8.5.8
2.8.5.9	2.8.6.1	2.8.6.2	2.8.6.3	2.8.6.4	2.8.6.5	2.8.6.6	2.8.6.7	2.8.6.8	2.8.6.9
2.8.7.1	2.8.7.2	2.8.7.3	2.8.7.4	2.8.7.5	2.8.7.6	2.8.7.7	2.8.7.8	2.8.7.9	2.8.8.1
2.8.8.2	2.8.8.3	2.8.8.4	2.8.8.5	2.8.8.6	2.8.8.7	2.8.8.8	2.8.8.9	2.8.9.1	2.8.9.2
2.8.9.3	2.8.9.4	2.8.9.5	2.8.9.6	2.8.9.7	2.8.9.8	2.8.9.9	2.9.1.1	2.9.1.2	2.9.1.3
2.9.1.4	2.9.1.5	2.9.1.6	2.9.1.7	2.9.1.8	2.9.1.9	2.9.2.1	2.9.2.2	2.9.2.3	2.9.2.4
2.9.2.5	2.9.2.6	2.9.2.7	2.9.2.8	2.9.2.9	2.9.3.1	2.9.3.2	2.9.3.3	2.9.3.4	2.9.3.5
2.9.3.6	2.9.3.7	2.9.3.8	2.9.3.9	2.9.4.1	2.9.4.2	2.9.4.3	2.9.4.4	2.9.4.5	2.9.4.6
2.9.4.7	2.9.4.8	2.9.4.9	2.9.5.1	2.9.5.2	2.9.5.3	2.9.5.4	2.9.5.5	2.9.5.6	2.9.5.7
2.9.5.8	2.9.5.9	2.9.6.1	2.9.6.2	2.9.6.3	2.9.6.4	2.9.6.5	2.9.6.6	2.9.6.7	2.9.6.8
2.9.6.9	2.9.7.1	2.9.7.2	2.9.7.3	2.9.7.4	2.9.7.5	2.9.7.6	2.9.7.7	2.9.7.8	2.9.7.9

Table 2 - continued

2.9.8.1	2.9.8.2	2.9.8.3	2.9.8.4	2.9.8.5	2.9.8.6	2.9.8.7	2.9.8.8	2.9.8.9	2.9.9.1
2.9.9.2	2.9.9.3	2.9.9.4	2.9.9.5	2.9.9.6	2.9.9.7	2.9.9.8	2.9.9.9	3.1.1.1	3.1.1.2
3.1.1.3	3.1.1.4	3.1.1.5	3.1.1.6	3.1.1.7	3.1.1.8	3.1.1.9	3.1.2.1	3.1.2.2	3.1.2.3
3.1.2.4	3.1.2.5	3.1.2.6	3.1.2.7	3.1.2.8	3.1.2.9	3.1.3.1	3.1.3.2	3.1.3.3	3.1.3.4
3.1.3.5	3.1.3.6	3.1.3.7	3.1.3.8	3.1.3.9	3.1.4.1	3.1.4.2	3.1.4.3	3.1.4.4	3.1.4.5
3.1.4.6	3.1.4.7	3.1.4.8	3.1.4.9	3.1.5.1	3.1.5.2	3.1.5.3	3.1.5.4	3.1.5.5	3.1.5.6
3.1.5.7	3.1.5.8	3.1.5.9	3.1.6.1	3.1.6.2	3.1.6.3	3.1.6.4	3.1.6.5	3.1.6.6	3.1.6.7
3.1.6.8	3.1.6.9	3.1.7.1	3.1.7.2	3.1.7.3	3.1.7.4	3.1.7.5	3.1.7.6	3.1.7.7	3.1.7.8
3.1.7.9	3.1.8.1	3.1.8.2	3.1.8.3	3.1.8.4	3.1.8.5	3.1.8.6	3.1.8.7	3.1.8.8	3.1.8.9
3.1.9.1	3.1.9.2	3.1.9.3	3.1.9.4	3.1.9.5	3.1.9.6	3.1.9.7	3.1.9.8	3.1.9.9	3.2.1.1
3.2.1.2	3.2.1.3	3.2.1.4	3.2.1.5	3.2.1.6	3.2.1.7	3.2.1.8	3.2.1.9	3.2.2.1	3.2.2.2
3.2.2.3	3.2.2.4	3.2.2.5	3.2.2.6	3.2.2.7	3.2.2.8	3.2.2.9	3.2.3.1	3.2.3.2	3.2.3.3
3.2.3.4	3.2.3.5	3.2.3.6	3.2.3.7	3.2.3.8	3.2.3.9	3.2.4.1	3.2.4.2	3.2.4.3	3.2.4.4
3.2.4.5	3.2.4.6	3.2.4.7	3.2.4.8	3.2.4.9	3.2.5.1	3.2.5.2	3.2.5.3	3.2.5.4	3.2.5.5
3.2.5.6	3.2.5.7	3.2.5.8	3.2.5.9	3.2.6.1	3.2.6.2	3.2.6.3	3.2.6.4	3.2.6.5	3.2.6.6
3.2.6.7	3.2.6.8	3.2.6.9	3.2.7.1	3.2.7.2	3.2.7.3	3.2.7.4	3.2.7.5	3.2.7.6	3.2.7.7
3.2.7.8	3.2.7.9	3.2.8.1	3.2.8.2	3.2.8.3	3.2.8.4	3.2.8.5	3.2.8.6	3.2.8.7	3.2.8.8
3.2.8.9	3.2.9.1	3.2.9.2	3.2.9.3	3.2.9.4	3.2.9.5	3.2.9.6	3.2.9.7	3.2.9.8	3.2.9.9
3.3.1.1	3.3.1.2	3.3.1.3	3.3.1.4	3.3.1.5	3.3.1.6	3.3.1.7	3.3.1.8	3.3.1.9	3.3.2.1
3.3.2.2	3.3.2.3	3.3.2.4	3.3.2.5	3.3.2.6	3.3.2.7	3.3.2.8	3.3.2.9	3.3.3.1	3.3.3.2
3.3.3.3	3.3.3.4	3.3.3.5	3.3.3.6	3.3.3.7	3.3.3.8	3.3.3.9	3.3.4.1	3.3.4.2	3.3.4.3
3.3.4.4	3.3.4.5	3.3.4.6	3.3.4.7	3.3.4.8	3.3.4.9	3.3.5.1	3.3.5.2	3.3.5.3	3.3.5.4
3.3.5.5	3.3.5.6	3.3.5.7	3.3.5.8	3.3.5.9	3.3.6.1	3.3.6.2	3.3.6.3	3.3.6.4	3.3.6.5
3.3.6.6	3.3.6.7	3.3.6.8	3.3.6.9	3.3.7.1	3.3.7.2	3.3.7.3	3.3.7.4	3.3.7.5	3.3.7.6
3.3.7.7	3.3.7.8	3.3.7.9	3.3.8.1	3.3.8.2	3.3.8.3	3.3.8.4	3.3.8.5	3.3.8.6	3.3.8.7
3.3.8.8	3.3.8.9	3.3.9.1	3.3.9.2	3.3.9.3	3.3.9.4	3.3.9.5	3.3.9.6	3.3.9.7	3.3.9.8
3.3.9.9	3.4.1.1	3.4.1.2	3.4.1.3	3.4.1.4	3.4.1.5	3.4.1.6	3.4.1.7	3.4.1.8	3.4.1.9
3.4.2.1	3.4.2.2	3.4.2.3	3.4.2.4	3.4.2.5	3.4.2.6	3.4.2.7	3.4.2.8	3.4.2.9	3.4.3.1
3.4.3.2	3.4.3.3	3.4.3.4	3.4.3.5	3.4.3.6	3.4.3.7	3.4.3.8	3.4.3.9	3.4.4.1	3.4.4.2
3.4.4.3	3.4.4.4	3.4.4.5	3.4.4.6	3.4.4.7	3.4.4.8	3.4.4.9	3.4.5.1	3.4.5.2	3.4.5.3
3.4.5.4	3.4.5.5	3.4.5.6	3.4.5.7	3.4.5.8	3.4.5.9	3.4.6.1	3.4.6.2	3.4.6.3	3.4.6.4
3.4.6.5	3.4.6.6	3.4.6.7	3.4.6.8	3.4.6.9	3.4.7.1	3.4.7.2	3.4.7.3	3.4.7.4	3.4.7.5
3.4.7.6	3.4.7.7	3.4.7.8	3.4.7.9	3.4.8.1	3.4.8.2	3.4.8.3	3.4.8.4	3.4.8.5	3.4.8.6
3.4.8.7	3.4.8.8	3.4.8.9	3.4.9.1	3.4.9.2	3.4.9.3	3.4.9.4	3.4.9.5	3.4.9.6	3.4.9.7
3.4.9.8	3.4.9.9	3.5.1.1	3.5.1.2	3.5.1.3	3.5.1.4	3.5.1.5	3.5.1.6	3.5.1.7	3.5.1.8
3.5.1.9	3.5.2.1	3.5.2.2	3.5.2.3	3.5.2.4	3.5.2.5	3.5.2.6	3.5.2.7	3.5.2.8	3.5.2.9
3.5.3.1	3.5.3.2	3.5.3.3	3.5.3.4	3.5.3.5	3.5.3.6	3.5.3.7	3.5.3.8	3.5.3.9	3.5.4.1
3.5.4.2	3.5.4.3	3.5.4.4	3.5.4.5	3.5.4.6	3.5.4.7	3.5.4.8	3.5.4.9	3.5.5.1	3.5.5.2
3.5.5.3	3.5.5.4	3.5.5.5	3.5.5.6	3.5.5.7	3.5.5.8	3.5.5.9	3.5.6.1	3.5.6.2	3.5.6.3
3.5.6.4	3.5.6.5	3.5.6.6	3.5.6.7	3.5.6.8	3.5.6.9	3.5.7.1	3.5.7.2	3.5.7.3	3.5.7.4
3.5.7.5	3.5.7.6	3.5.7.7	3.5.7.8	3.5.7.9	3.5.8.1	3.5.8.2	3.5.8.3	3.5.8.4	3.5.8.5
3.5.8.6	3.5.8.7	3.5.8.8	3.5.8.9	3.5.9.1	3.5.9.2	3.5.9.3	3.5.9.4	3.5.9.5	3.5.9.6
3.5.9.7	3.5.9.8	3.5.9.9	3.6.1.1	3.6.1.2	3.6.1.3	3.6.1.4	3.6.1.5	3.6.1.6	3.6.1.7
3.6.1.8	3.6.1.9	3.6.2.1	3.6.2.2	3.6.2.3	3.6.2.4	3.6.2.5	3.6.2.6	3.6.2.7	3.6.2.8
3.6.2.9	3.6.3.1	3.6.3.2	3.6.3.3	3.6.3.4	3.6.3.5	3.6.3.6	3.6.3.7	3.6.3.8	3.6.3.9
3.6.4.1	3.6.4.2	3.6.4.3	3.6.4.4	3.6.4.5	3.6.4.6	3.6.4.7	3.6.4.8	3.6.4.9	3.6.5.1
3.6.5.2	3.6.5.3	3.6.5.4	3.6.5.5	3.6.5.6	3.6.5.7	3.6.5.8	3.6.5.9	3.6.6.1	3.6.6.2
3.6.6.3	3.6.6.4	3.6.6.5	3.6.6.6	3.6.6.7	3.6.6.8	3.6.6.9	3.6.7.1	3.6.7.2	3.6.7.3

Table 2 - continued

3.6.7.4	3.6.7.5	3.6.7.6	3.6.7.7	3.6.7.8	3.6.7.9	3.6.8.1	3.6.8.2	3.6.8.3	3.6.8.4
3.6.8.5	3.6.8.6	3.6.8.7	3.6.8.8	3.6.8.9	3.6.9.1	3.6.9.2	3.6.9.3	3.6.9.4	3.6.9.5
3.6.9.6	3.6.9.7	3.6.9.8	3.6.9.9	3.7.1.1	3.7.1.2	3.7.1.3	3.7.1.4	3.7.1.5	3.7.1.6
3.7.1.7	3.7.1.8	3.7.1.9	3.7.2.1	3.7.2.2	3.7.2.3	3.7.2.4	3.7.2.5	3.7.2.6	3.7.2.7
3.7.2.8	3.7.2.9	3.7.3.1	3.7.3.2	3.7.3.3	3.7.3.4	3.7.3.5	3.7.3.6	3.7.3.7	3.7.3.8
3.7.3.9	3.7.4.1	3.7.4.2	3.7.4.3	3.7.4.4	3.7.4.5	3.7.4.6	3.7.4.7	3.7.4.8	3.7.4.9
3.7.5.1	3.7.5.2	3.7.5.3	3.7.5.4	3.7.5.5	3.7.5.6	3.7.5.7	3.7.5.8	3.7.5.9	3.7.6.1
3.7.6.2	3.7.6.3	3.7.6.4	3.7.6.5	3.7.6.6	3.7.6.7	3.7.6.8	3.7.6.9	3.7.7.1	3.7.7.2
3.7.7.3	3.7.7.4	3.7.7.5	3.7.7.6	3.7.7.7	3.7.7.8	3.7.7.9	3.7.8.1	3.7.8.2	3.7.8.3
3.7.8.4	3.7.8.5	3.7.8.6	3.7.8.7	3.7.8.8	3.7.8.9	3.7.9.1	3.7.9.2	3.7.9.3	3.7.9.4
3.7.9.5	3.7.9.6	3.7.9.7	3.7.9.8	3.7.9.9	3.8.1.1	3.8.1.2	3.8.1.3	3.8.1.4	3.8.1.5
3.8.1.6	3.8.1.7	3.8.1.8	3.8.1.9	3.8.2.1	3.8.2.2	3.8.2.3	3.8.2.4	3.8.2.5	3.8.2.6
3.8.2.7	3.8.2.8	3.8.2.9	3.8.3.1	3.8.3.2	3.8.3.3	3.8.3.4	3.8.3.5	3.8.3.6	3.8.3.7
3.8.3.8	3.8.3.9	3.8.4.1	3.8.4.2	3.8.4.3	3.8.4.4	3.8.4.5	3.8.4.6	3.8.4.7	3.8.4.8
3.8.4.9	3.8.5.1	3.8.5.2	3.8.5.3	3.8.5.4	3.8.5.5	3.8.5.6	3.8.5.7	3.8.5.8	3.8.5.9
3.8.6.1	3.8.6.2	3.8.6.3	3.8.6.4	3.8.6.5	3.8.6.6	3.8.6.7	3.8.6.8	3.8.6.9	3.8.7.1
3.8.7.2	3.8.7.3	3.8.7.4	3.8.7.5	3.8.7.6	3.8.7.7	3.8.7.8	3.8.7.9	3.8.8.1	3.8.8.2
3.8.8.3	3.8.8.4	3.8.8.5	3.8.8.6	3.8.8.7	3.8.8.8	3.8.8.9	3.8.9.1	3.8.9.2	3.8.9.3
3.8.9.4	3.8.9.5	3.8.9.6	3.8.9.7	3.8.9.8	3.8.9.9	3.9.1.1	3.9.1.2	3.9.1.3	3.9.1.4
3.9.1.5	3.9.1.6	3.9.1.7	3.9.1.8	3.9.1.9	3.9.2.1	3.9.2.2	3.9.2.3	3.9.2.4	3.9.2.5
3.9.2.6	3.9.2.7	3.9.2.8	3.9.2.9	3.9.3.1	3.9.3.2	3.9.3.3	3.9.3.4	3.9.3.5	3.9.3.6
3.9.3.7	3.9.3.8	3.9.3.9	3.9.4.1	3.9.4.2	3.9.4.3	3.9.4.4	3.9.4.5	3.9.4.6	3.9.4.7
3.9.4.8	3.9.4.9	3.9.5.1	3.9.5.2	3.9.5.3	3.9.5.4	3.9.5.5	3.9.5.6	3.9.5.7	3.9.5.8
3.9.5.9	3.9.6.1	3.9.6.2	3.9.6.3	3.9.6.4	3.9.6.5	3.9.6.6	3.9.6.7	3.9.6.8	3.9.6.9
3.9.7.1	3.9.7.2	3.9.7.3	3.9.7.4	3.9.7.5	3.9.7.6	3.9.7.7	3.9.7.8	3.9.7.9	3.9.8.1
3.9.8.2	3.9.8.3	3.9.8.4	3.9.8.5	3.9.8.6	3.9.8.7	3.9.8.8	3.9.8.9	3.9.9.1	3.9.9.2
3.9.9.3	3.9.9.4	3.9.9.5	3.9.9.6	3.9.9.7	3.9.9.8	3.9.9.9	4.1.1.1	4.1.1.2	4.1.1.3
4.1.1.4	4.1.1.5	4.1.1.6	4.1.1.7	4.1.1.8	4.1.1.9	4.1.2.1	4.1.2.2	4.1.2.3	4.1.2.4
4.1.2.5	4.1.2.6	4.1.2.7	4.1.2.8	4.1.2.9	4.1.3.1	4.1.3.2	4.1.3.3	4.1.3.4	4.1.3.5
4.1.3.6	4.1.3.7	4.1.3.8	4.1.3.9	4.1.4.1	4.1.4.2	4.1.4.3	4.1.4.4	4.1.4.5	4.1.4.6
4.1.4.7	4.1.4.8	4.1.4.9	4.1.5.1	4.1.5.2	4.1.5.3	4.1.5.4	4.1.5.5	4.1.5.6	4.1.5.7
4.1.5.8	4.1.5.9	4.1.6.1	4.1.6.2	4.1.6.3	4.1.6.4	4.1.6.5	4.1.6.6	4.1.6.7	4.1.6.8
4.1.6.9	4.1.7.1	4.1.7.2	4.1.7.3	4.1.7.4	4.1.7.5	4.1.7.6	4.1.7.7	4.1.7.8	4.1.7.9
4.1.8.1	4.1.8.2	4.1.8.3	4.1.8.4	4.1.8.5	4.1.8.6	4.1.8.7	4.1.8.8	4.1.8.9	4.1.9.1
4.1.9.2	4.1.9.3	4.1.9.4	4.1.9.5	4.1.9.6	4.1.9.7	4.1.9.8	4.1.9.9	4.2.1.1	4.2.1.2
4.2.1.3	4.2.1.4	4.2.1.5	4.2.1.6	4.2.1.7	4.2.1.8	4.2.1.9	4.2.2.1	4.2.2.2	4.2.2.3
4.2.2.4	4.2.2.5	4.2.2.6	4.2.2.7	4.2.2.8	4.2.2.9	4.2.3.1	4.2.3.2	4.2.3.3	4.2.3.4
4.2.3.5	4.2.3.6	4.2.3.7	4.2.3.8	4.2.3.9	4.2.4.1	4.2.4.2	4.2.4.3	4.2.4.4	4.2.4.5
4.2.4.6	4.2.4.7	4.2.4.8	4.2.4.9	4.2.5.1	4.2.5.2	4.2.5.3	4.2.5.4	4.2.5.5	4.2.5.6
4.2.5.7	4.2.5.8	4.2.5.9	4.2.6.1	4.2.6.2	4.2.6.3	4.2.6.4	4.2.6.5	4.2.6.6	4.2.6.7
4.2.6.8	4.2.6.9	4.2.7.1	4.2.7.2	4.2.7.3	4.2.7.4	4.2.7.5	4.2.7.6	4.2.7.7	4.2.7.8
4.2.7.9	4.2.8.1	4.2.8.2	4.2.8.3	4.2.8.4	4.2.8.5	4.2.8.6	4.2.8.7	4.2.8.8	4.2.8.9
4.2.9.1	4.2.9.2	4.2.9.3	4.2.9.4	4.2.9.5	4.2.9.6	4.2.9.7	4.2.9.8	4.2.9.9	4.3.1.1
4.3.1.2	4.3.1.3	4.3.1.4	4.3.1.5	4.3.1.6	4.3.1.7	4.3.1.8	4.3.1.9	4.3.2.1	4.3.2.2
4.3.2.3	4.3.2.4	4.3.2.5	4.3.2.6	4.3.2.7	4.3.2.8	4.3.2.9	4.3.3.1	4.3.3.2	4.3.3.3
4.3.3.4	4.3.3.5	4.3.3.6	4.3.3.7	4.3.3.8	4.3.3.9	4.3.4.1	4.3.4.2	4.3.4.3	4.3.4.4
4.3.4.5	4.3.4.6	4.3.4.7	4.3.4.8	4.3.4.9	4.3.5.1	4.3.5.2	4.3.5.3	4.3.5.4	4.3.5.5
4.3.5.6	4.3.5.7	4.3.5.8	4.3.5.9	4.3.6.1	4.3.6.2	4.3.6.3	4.3.6.4	4.3.6.5	4.3.6.6

Table 2 - continued

4.3.6.7	4.3.6.8	4.3.6.9	4.3.7.1	4.3.7.2	4.3.7.3	4.3.7.4	4.3.7.5	4.3.7.6	4.3.7.7
4.3.7.8	4.3.7.9	4.3.8.1	4.3.8.2	4.3.8.3	4.3.8.4	4.3.8.5	4.3.8.6	4.3.8.7	4.3.8.8
4.3.8.9	4.3.9.1	4.3.9.2	4.3.9.3	4.3.9.4	4.3.9.5	4.3.9.6	4.3.9.7	4.3.9.8	4.3.9.9
4.4.1.1	4.4.1.2	4.4.1.3	4.4.1.4	4.4.1.5	4.4.1.6	4.4.1.7	4.4.1.8	4.4.1.9	4.4.2.1
4.4.2.2	4.4.2.3	4.4.2.4	4.4.2.5	4.4.2.6	4.4.2.7	4.4.2.8	4.4.2.9	4.4.3.1	4.4.3.2
4.4.3.3	4.4.3.4	4.4.3.5	4.4.3.6	4.4.3.7	4.4.3.8	4.4.3.9	4.4.4.1	4.4.4.2	4.4.4.3
4.4.4.4	4.4.4.5	4.4.4.6	4.4.4.7	4.4.4.8	4.4.4.9	4.4.5.1	4.4.5.2	4.4.5.3	4.4.5.4
4.4.5.5	4.4.5.6	4.4.5.7	4.4.5.8	4.4.5.9	4.4.6.1	4.4.6.2	4.4.6.3	4.4.6.4	4.4.6.5
4.4.6.6	4.4.6.7	4.4.6.8	4.4.6.9	4.4.7.1	4.4.7.2	4.4.7.3	4.4.7.4	4.4.7.5	4.4.7.6
4.4.7.7	4.4.7.8	4.4.7.9	4.4.8.1	4.4.8.2	4.4.8.3	4.4.8.4	4.4.8.5	4.4.8.6	4.4.8.7
4.4.8.8	4.4.8.9	4.4.9.1	4.4.9.2	4.4.9.3	4.4.9.4	4.4.9.5	4.4.9.6	4.4.9.7	4.4.9.8
4.4.9.9	4.5.1.1	4.5.1.2	4.5.1.3	4.5.1.4	4.5.1.5	4.5.1.6	4.5.1.7	4.5.1.8	4.5.1.9
4.5.2.1	4.5.2.2	4.5.2.3	4.5.2.4	4.5.2.5	4.5.2.6	4.5.2.7	4.5.2.8	4.5.2.9	4.5.3.1
4.5.3.2	4.5.3.3	4.5.3.4	4.5.3.5	4.5.3.6	4.5.3.7	4.5.3.8	4.5.3.9	4.5.4.1	4.5.4.2
4.5.4.3	4.5.4.4	4.5.4.5	4.5.4.6	4.5.4.7	4.5.4.8	4.5.4.9	4.5.5.1	4.5.5.2	4.5.5.3
4.5.5.4	4.5.5.5	4.5.5.6	4.5.5.7	4.5.5.8	4.5.5.9	4.5.6.1	4.5.6.2	4.5.6.3	4.5.6.4
4.5.6.5	4.5.6.6	4.5.6.7	4.5.6.8	4.5.6.9	4.5.7.1	4.5.7.2	4.5.7.3	4.5.7.4	4.5.7.5
4.5.7.6	4.5.7.7	4.5.7.8	4.5.7.9	4.5.8.1	4.5.8.2	4.5.8.3	4.5.8.4	4.5.8.5	4.5.8.6
4.5.8.7	4.5.8.8	4.5.8.9	4.5.9.1	4.5.9.2	4.5.9.3	4.5.9.4	4.5.9.5	4.5.9.6	4.5.9.7
4.5.9.8	4.5.9.9	4.6.1.1	4.6.1.2	4.6.1.3	4.6.1.4	4.6.1.5	4.6.1.6	4.6.1.7	4.6.1.8
4.6.1.9	4.6.2.1	4.6.2.2	4.6.2.3	4.6.2.4	4.6.2.5	4.6.2.6	4.6.2.7	4.6.2.8	4.6.2.9
4.6.3.1	4.6.3.2	4.6.3.3	4.6.3.4	4.6.3.5	4.6.3.6	4.6.3.7	4.6.3.8	4.6.3.9	4.6.4.1
4.6.4.2	4.6.4.3	4.6.4.4	4.6.4.5	4.6.4.6	4.6.4.7	4.6.4.8	4.6.4.9	4.6.5.1	4.6.5.2
4.6.5.3	4.6.5.4	4.6.5.5	4.6.5.6	4.6.5.7	4.6.5.8	4.6.5.9	4.6.6.1	4.6.6.2	4.6.6.3
4.6.6.4	4.6.6.5	4.6.6.6	4.6.6.7	4.6.6.8	4.6.6.9	4.6.7.1	4.6.7.2	4.6.7.3	4.6.7.4
4.6.7.5	4.6.7.6	4.6.7.7	4.6.7.8	4.6.7.9	4.6.8.1	4.6.8.2	4.6.8.3	4.6.8.4	4.6.8.5
4.6.8.6	4.6.8.7	4.6.8.8	4.6.8.9	4.6.9.1	4.6.9.2	4.6.9.3	4.6.9.4	4.6.9.5	4.6.9.6
4.6.9.7	4.6.9.8	4.6.9.9	4.7.1.1	4.7.1.2	4.7.1.3	4.7.1.4	4.7.1.5	4.7.1.6	4.7.1.7
4.7.1.8	4.7.1.9	4.7.2.1	4.7.2.2	4.7.2.3	4.7.2.4	4.7.2.5	4.7.2.6	4.7.2.7	4.7.2.8
4.7.2.9	4.7.3.1	4.7.3.2	4.7.3.3	4.7.3.4	4.7.3.5	4.7.3.6	4.7.3.7	4.7.3.8	4.7.3.9
4.7.4.1	4.7.4.2	4.7.4.3	4.7.4.4	4.7.4.5	4.7.4.6	4.7.4.7	4.7.4.8	4.7.4.9	4.7.5.1
4.7.5.2	4.7.5.3	4.7.5.4	4.7.5.5	4.7.5.6	4.7.5.7	4.7.5.8	4.7.5.9	4.7.6.1	4.7.6.2
4.7.6.3	4.7.6.4	4.7.6.5	4.7.6.6	4.7.6.7	4.7.6.8	4.7.6.9	4.7.7.1	4.7.7.2	4.7.7.3
4.7.7.4	4.7.7.5	4.7.7.6	4.7.7.7	4.7.7.8	4.7.7.9	4.7.8.1	4.7.8.2	4.7.8.3	4.7.8.4
4.7.8.5	4.7.8.6	4.7.8.7	4.7.8.8	4.7.8.9	4.7.9.1	4.7.9.2	4.7.9.3	4.7.9.4	4.7.9.5
4.7.9.6	4.7.9.7	4.7.9.8	4.7.9.9	4.8.1.1	4.8.1.2	4.8.1.3	4.8.1.4	4.8.1.5	4.8.1.6
4.8.1.7	4.8.1.8	4.8.1.9	4.8.2.1	4.8.2.2	4.8.2.3	4.8.2.4	4.8.2.5	4.8.2.6	4.8.2.7
4.8.2.8	4.8.2.9	4.8.3.1	4.8.3.2	4.8.3.3	4.8.3.4	4.8.3.5	4.8.3.6	4.8.3.7	4.8.3.8
4.8.3.9	4.8.4.1	4.8.4.2	4.8.4.3	4.8.4.4	4.8.4.5	4.8.4.6	4.8.4.7	4.8.4.8	4.8.4.9
4.8.5.1	4.8.5.2	4.8.5.3	4.8.5.4	4.8.5.5	4.8.5.6	4.8.5.7	4.8.5.8	4.8.5.9	4.8.6.1
4.8.6.2	4.8.6.3	4.8.6.4	4.8.6.5	4.8.6.6	4.8.6.7	4.8.6.8	4.8.6.9	4.8.7.1	4.8.7.2
4.8.7.3	4.8.7.4	4.8.7.5	4.8.7.6	4.8.7.7	4.8.7.8	4.8.7.9	4.8.8.1	4.8.8.2	4.8.8.3
4.8.8.4	4.8.8.5	4.8.8.6	4.8.8.7	4.8.8.8	4.8.8.9	4.8.9.1	4.8.9.2	4.8.9.3	4.8.9.4
4.8.9.5	4.8.9.6	4.8.9.7	4.8.9.8	4.8.9.9	4.9.1.1	4.9.1.2	4.9.1.3	4.9.1.4	4.9.1.5
4.9.1.6	4.9.1.7	4.9.1.8	4.9.1.9	4.9.2.1	4.9.2.2	4.9.2.3	4.9.2.4	4.9.2.5	4.9.2.6
4.9.2.7	4.9.2.8	4.9.2.9	4.9.3.1	4.9.3.2	4.9.3.3	4.9.3.4	4.9.3.5	4.9.3.6	4.9.3.7
4.9.3.8	4.9.3.9	4.9.4.1	4.9.4.2	4.9.4.3	4.9.4.4	4.9.4.5	4.9.4.6	4.9.4.7	4.9.4.8
4.9.4.9	4.9.5.1	4.9.5.2	4.9.5.3	4.9.5.4	4.9.5.5	4.9.5.6	4.9.5.7	4.9.5.8	4.9.5.9

Table 2 - continued

4.9.6.1	4.9.6.2	4.9.6.3	4.9.6.4	4.9.6.5	4.9.6.6	4.9.6.7	4.9.6.8	4.9.6.9	4.9.7.1
4.9.7.2	4.9.7.3	4.9.7.4	4.9.7.5	4.9.7.6	4.9.7.7	4.9.7.8	4.9.7.9	4.9.8.1	4.9.8.2
4.9.8.3	4.9.8.4	4.9.8.5	4.9.8.6	4.9.8.7	4.9.8.8	4.9.8.9	4.9.9.1	4.9.9.2	4.9.9.3
4.9.9.4	4.9.9.5	4.9.9.6	4.9.9.7	4.9.9.8	4.9.9.9	5.1.1.1	5.1.1.2	5.1.1.3	5.1.1.4
5.1.1.5	5.1.1.6	5.1.1.7	5.1.1.8	5.1.1.9	5.1.2.1	5.1.2.2	5.1.2.3	5.1.2.4	5.1.2.5
5.1.2.6	5.1.2.7	5.1.2.8	5.1.2.9	5.1.3.1	5.1.3.2	5.1.3.3	5.1.3.4	5.1.3.5	5.1.3.6
5.1.3.7	5.1.3.8	5.1.3.9	5.1.4.1	5.1.4.2	5.1.4.3	5.1.4.4	5.1.4.5	5.1.4.6	5.1.4.7
5.1.4.8	5.1.4.9	5.1.5.1	5.1.5.2	5.1.5.3	5.1.5.4	5.1.5.5	5.1.5.6	5.1.5.7	5.1.5.8
5.1.5.9	5.1.6.1	5.1.6.2	5.1.6.3	5.1.6.4	5.1.6.5	5.1.6.6	5.1.6.7	5.1.6.8	5.1.6.9
5.1.7.1	5.1.7.2	5.1.7.3	5.1.7.4	5.1.7.5	5.1.7.6	5.1.7.7	5.1.7.8	5.1.7.9	5.1.8.1
5.1.8.2	5.1.8.3	5.1.8.4	5.1.8.5	5.1.8.6	5.1.8.7	5.1.8.8	5.1.8.9	5.1.9.1	5.1.9.2
5.1.9.3	5.1.9.4	5.1.9.5	5.1.9.6	5.1.9.7	5.1.9.8	5.1.9.9	5.2.1.1	5.2.1.2	5.2.1.3
5.2.1.4	5.2.1.5	5.2.1.6	5.2.1.7	5.2.1.8	5.2.1.9	5.2.2.1	5.2.2.2	5.2.2.3	5.2.2.4
5.2.2.5	5.2.2.6	5.2.2.7	5.2.2.8	5.2.2.9	5.2.3.1	5.2.3.2	5.2.3.3	5.2.3.4	5.2.3.5
5.2.3.6	5.2.3.7	5.2.3.8	5.2.3.9	5.2.4.1	5.2.4.2	5.2.4.3	5.2.4.4	5.2.4.5	5.2.4.6
5.2.4.7	5.2.4.8	5.2.4.9	5.2.5.1	5.2.5.2	5.2.5.3	5.2.5.4	5.2.5.5	5.2.5.6	5.2.5.7
5.2.5.8	5.2.5.9	5.2.6.1	5.2.6.2	5.2.6.3	5.2.6.4	5.2.6.5	5.2.6.6	5.2.6.7	5.2.6.8
5.2.6.9	5.2.7.1	5.2.7.2	5.2.7.3	5.2.7.4	5.2.7.5	5.2.7.6	5.2.7.7	5.2.7.8	5.2.7.9
5.2.8.1	5.2.8.2	5.2.8.3	5.2.8.4	5.2.8.5	5.2.8.6	5.2.8.7	5.2.8.8	5.2.8.9	5.2.9.1
5.2.9.2	5.2.9.3	5.2.9.4	5.2.9.5	5.2.9.6	5.2.9.7	5.2.9.8	5.2.9.9	5.3.1.1	5.3.1.2
5.3.1.3	5.3.1.4	5.3.1.5	5.3.1.6	5.3.1.7	5.3.1.8	5.3.1.9	5.3.2.1	5.3.2.2	5.3.2.3
5.3.2.4	5.3.2.5	5.3.2.6	5.3.2.7	5.3.2.8	5.3.2.9	5.3.3.1	5.3.3.2	5.3.3.3	5.3.3.4
5.3.3.5	5.3.3.6	5.3.3.7	5.3.3.8	5.3.3.9	5.3.4.1	5.3.4.2	5.3.4.3	5.3.4.4	5.3.4.5
5.3.4.6	5.3.4.7	5.3.4.8	5.3.4.9	5.3.5.1	5.3.5.2	5.3.5.3	5.3.5.4	5.3.5.5	5.3.5.6
5.3.5.7	5.3.5.8	5.3.5.9	5.3.6.1	5.3.6.2	5.3.6.3	5.3.6.4	5.3.6.5	5.3.6.6	5.3.6.7
5.3.6.8	5.3.6.9	5.3.7.1	5.3.7.2	5.3.7.3	5.3.7.4	5.3.7.5	5.3.7.6	5.3.7.7	5.3.7.8
5.3.7.9	5.3.8.1	5.3.8.2	5.3.8.3	5.3.8.4	5.3.8.5	5.3.8.6	5.3.8.7	5.3.8.8	5.3.8.9
5.3.9.1	5.3.9.2	5.3.9.3	5.3.9.4	5.3.9.5	5.3.9.6	5.3.9.7	5.3.9.8	5.3.9.9	5.4.1.1
5.4.1.2	5.4.1.3	5.4.1.4	5.4.1.5	5.4.1.6	5.4.1.7	5.4.1.8	5.4.1.9	5.4.2.1	5.4.2.2
5.4.2.3	5.4.2.4	5.4.2.5	5.4.2.6	5.4.2.7	5.4.2.8	5.4.2.9	5.4.3.1	5.4.3.2	5.4.3.3
5.4.3.4	5.4.3.5	5.4.3.6	5.4.3.7	5.4.3.8	5.4.3.9	5.4.4.1	5.4.4.2	5.4.4.3	5.4.4.4
5.4.4.5	5.4.4.6	5.4.4.7	5.4.4.8	5.4.4.9	5.4.5.1	5.4.5.2	5.4.5.3	5.4.5.4	5.4.5.5
5.4.5.6	5.4.5.7	5.4.5.8	5.4.5.9	5.4.6.1	5.4.6.2	5.4.6.3	5.4.6.4	5.4.6.5	5.4.6.6
5.4.6.7	5.4.6.8	5.4.6.9	5.4.7.1	5.4.7.2	5.4.7.3	5.4.7.4	5.4.7.5	5.4.7.6	5.4.7.7
5.4.7.8	5.4.7.9	5.4.8.1	5.4.8.2	5.4.8.3	5.4.8.4	5.4.8.5	5.4.8.6	5.4.8.7	5.4.8.8
5.4.8.9	5.4.9.1	5.4.9.2	5.4.9.3	5.4.9.4	5.4.9.5	5.4.9.6	5.4.9.7	5.4.9.8	5.4.9.9
5.5.1.1	5.5.1.2	5.5.1.3	5.5.1.4	5.5.1.5	5.5.1.6	5.5.1.7	5.5.1.8	5.5.1.9	5.5.2.1
5.5.2.2	5.5.2.3	5.5.2.4	5.5.2.5	5.5.2.6	5.5.2.7	5.5.2.8	5.5.2.9	5.5.3.1	5.5.3.2
5.5.3.3	5.5.3.4	5.5.3.5	5.5.3.6	5.5.3.7	5.5.3.8	5.5.3.9	5.5.4.1	5.5.4.2	5.5.4.3
5.5.4.4	5.5.4.5	5.5.4.6	5.5.4.7	5.5.4.8	5.5.4.9	5.5.5.1	5.5.5.2	5.5.5.3	5.5.5.4
5.5.5.5	5.5.5.6	5.5.5.7	5.5.5.8	5.5.5.9	5.5.6.1	5.5.6.2	5.5.6.3	5.5.6.4	5.5.6.5
5.5.6.6	5.5.6.7	5.5.6.8	5.5.6.9	5.5.7.1	5.5.7.2	5.5.7.3	5.5.7.4	5.5.7.5	5.5.7.6
5.5.7.7	5.5.7.8	5.5.7.9	5.5.8.1	5.5.8.2	5.5.8.3	5.5.8.4	5.5.8.5	5.5.8.6	5.5.8.7
5.5.8.8	5.5.8.9	5.5.9.1	5.5.9.2	5.5.9.3	5.5.9.4	5.5.9.5	5.5.9.6	5.5.9.7	5.5.9.8
5.5.9.9	5.6.1.1	5.6.1.2	5.6.1.3	5.6.1.4	5.6.1.5	5.6.1.6	5.6.1.7	5.6.1.8	5.6.1.9
5.6.2.1	5.6.2.2	5.6.2.3	5.6.2.4	5.6.2.5	5.6.2.6	5.6.2.7	5.6.2.8	5.6.2.9	5.6.3.1
5.6.3.2	5.6.3.3	5.6.3.4	5.6.3.5	5.6.3.6	5.6.3.7	5.6.3.8	5.6.3.9	5.6.4.1	5.6.4.2
5.6.4.3	5.6.4.4	5.6.4.5	5.6.4.6	5.6.4.7	5.6.4.8	5.6.4.9	5.6.5.1	5.6.5.2	5.6.5.3

Table 2 - continued

5.6.5.4	5.6.5.5	5.6.5.6	5.6.5.7	5.6.5.8	5.6.5.9	5.6.6.1	5.6.6.2	5.6.6.3	5.6.6.4
5.6.6.5	5.6.6.6	5.6.6.7	5.6.6.8	5.6.6.9	5.6.7.1	5.6.7.2	5.6.7.3	5.6.7.4	5.6.7.5
5.6.7.6	5.6.7.7	5.6.7.8	5.6.7.9	5.6.8.1	5.6.8.2	5.6.8.3	5.6.8.4	5.6.8.5	5.6.8.6
5.6.8.7	5.6.8.8	5.6.8.9	5.6.9.1	5.6.9.2	5.6.9.3	5.6.9.4	5.6.9.5	5.6.9.6	5.6.9.7
5.6.9.8	5.6.9.9	5.7.1.1	5.7.1.2	5.7.1.3	5.7.1.4	5.7.1.5	5.7.1.6	5.7.1.7	5.7.1.8
5.7.1.9	5.7.2.1	5.7.2.2	5.7.2.3	5.7.2.4	5.7.2.5	5.7.2.6	5.7.2.7	5.7.2.8	5.7.2.9
5.7.3.1	5.7.3.2	5.7.3.3	5.7.3.4	5.7.3.5	5.7.3.6	5.7.3.7	5.7.3.8	5.7.3.9	5.7.4.1
5.7.4.2	5.7.4.3	5.7.4.4	5.7.4.5	5.7.4.6	5.7.4.7	5.7.4.8	5.7.4.9	5.7.5.1	5.7.5.2
5.7.5.3	5.7.5.4	5.7.5.5	5.7.5.6	5.7.5.7	5.7.5.8	5.7.5.9	5.7.6.1	5.7.6.2	5.7.6.3
5.7.6.4	5.7.6.5	5.7.6.6	5.7.6.7	5.7.6.8	5.7.6.9	5.7.7.1	5.7.7.2	5.7.7.3	5.7.7.4
5.7.7.5	5.7.7.6	5.7.7.7	5.7.7.8	5.7.7.9	5.7.8.1	5.7.8.2	5.7.8.3	5.7.8.4	5.7.8.5
5.7.8.6	5.7.8.7	5.7.8.8	5.7.8.9	5.7.9.1	5.7.9.2	5.7.9.3	5.7.9.4	5.7.9.5	5.7.9.6
5.7.9.7	5.7.9.8	5.7.9.9	5.8.1.1	5.8.1.2	5.8.1.3	5.8.1.4	5.8.1.5	5.8.1.6	5.8.1.7
5.8.1.8	5.8.1.9	5.8.2.1	5.8.2.2	5.8.2.3	5.8.2.4	5.8.2.5	5.8.2.6	5.8.2.7	5.8.2.8
5.8.2.9	5.8.3.1	5.8.3.2	5.8.3.3	5.8.3.4	5.8.3.5	5.8.3.6	5.8.3.7	5.8.3.8	5.8.3.9
5.8.4.1	5.8.4.2	5.8.4.3	5.8.4.4	5.8.4.5	5.8.4.6	5.8.4.7	5.8.4.8	5.8.4.9	5.8.5.1
5.8.5.2	5.8.5.3	5.8.5.4	5.8.5.5	5.8.5.6	5.8.5.7	5.8.5.8	5.8.5.9	5.8.6.1	5.8.6.2
5.8.6.3	5.8.6.4	5.8.6.5	5.8.6.6	5.8.6.7	5.8.6.8	5.8.6.9	5.8.7.1	5.8.7.2	5.8.7.3
5.8.7.4	5.8.7.5	5.8.7.6	5.8.7.7	5.8.7.8	5.8.7.9	5.8.8.1	5.8.8.2	5.8.8.3	5.8.8.4
5.8.8.5	5.8.8.6	5.8.8.7	5.8.8.8	5.8.8.9	5.8.9.1	5.8.9.2	5.8.9.3	5.8.9.4	5.8.9.5
5.8.9.6	5.8.9.7	5.8.9.8	5.8.9.9	5.9.1.1	5.9.1.2	5.9.1.3	5.9.1.4	5.9.1.5	5.9.1.6
5.9.1.7	5.9.1.8	5.9.1.9	5.9.2.1	5.9.2.2	5.9.2.3	5.9.2.4	5.9.2.5	5.9.2.6	5.9.2.7
5.9.2.8	5.9.2.9	5.9.3.1	5.9.3.2	5.9.3.3	5.9.3.4	5.9.3.5	5.9.3.6	5.9.3.7	5.9.3.8
5.9.3.9	5.9.4.1	5.9.4.2	5.9.4.3	5.9.4.4	5.9.4.5	5.9.4.6	5.9.4.7	5.9.4.8	5.9.4.9
5.9.5.1	5.9.5.2	5.9.5.3	5.9.5.4	5.9.5.5	5.9.5.6	5.9.5.7	5.9.5.8	5.9.5.9	5.9.6.1
5.9.6.2	5.9.6.3	5.9.6.4	5.9.6.5	5.9.6.6	5.9.6.7	5.9.6.8	5.9.6.9	5.9.7.1	5.9.7.2
5.9.7.3	5.9.7.4	5.9.7.5	5.9.7.6	5.9.7.7	5.9.7.8	5.9.7.9	5.9.8.1	5.9.8.2	5.9.8.3
5.9.8.4	5.9.8.5	5.9.8.6	5.9.8.7	5.9.8.8	5.9.8.9	5.9.9.1	5.9.9.2	5.9.9.3	5.9.9.4
5.9.9.5	5.9.9.6	5.9.9.7	5.9.9.8	5.9.9.9	6.1.1.1	6.1.1.2	6.1.1.3	6.1.1.4	6.1.1.5
6.1.1.6	6.1.1.7	6.1.1.8	6.1.1.9	6.1.2.1	6.1.2.2	6.1.2.3	6.1.2.4	6.1.2.5	6.1.2.6
6.1.2.7	6.1.2.8	6.1.2.9	6.1.3.1	6.1.3.2	6.1.3.3	6.1.3.4	6.1.3.5	6.1.3.6	6.1.3.7
6.1.3.8	6.1.3.9	6.1.4.1	6.1.4.2	6.1.4.3	6.1.4.4	6.1.4.5	6.1.4.6	6.1.4.7	6.1.4.8
6.1.4.9	6.1.5.1	6.1.5.2	6.1.5.3	6.1.5.4	6.1.5.5	6.1.5.6	6.1.5.7	6.1.5.8	6.1.5.9
6.1.6.1	6.1.6.2	6.1.6.3	6.1.6.4	6.1.6.5	6.1.6.6	6.1.6.7	6.1.6.8	6.1.6.9	6.1.7.1
6.1.7.2	6.1.7.3	6.1.7.4	6.1.7.5	6.1.7.6	6.1.7.7	6.1.7.8	6.1.7.9	6.1.8.1	6.1.8.2
6.1.8.3	6.1.8.4	6.1.8.5	6.1.8.6	6.1.8.7	6.1.8.8	6.1.8.9	6.1.9.1	6.1.9.2	6.1.9.3
6.1.9.4	6.1.9.5	6.1.9.6	6.1.9.7	6.1.9.8	6.1.9.9	6.2.1.1	6.2.1.2	6.2.1.3	6.2.1.4
6.2.1.5	6.2.1.6	6.2.1.7	6.2.1.8	6.2.1.9	6.2.2.1	6.2.2.2	6.2.2.3	6.2.2.4	6.2.2.5
6.2.2.6	6.2.2.7	6.2.2.8	6.2.2.9	6.2.3.1	6.2.3.2	6.2.3.3	6.2.3.4	6.2.3.5	6.2.3.6
6.2.3.7	6.2.3.8	6.2.3.9	6.2.4.1	6.2.4.2	6.2.4.3	6.2.4.4	6.2.4.5	6.2.4.6	6.2.4.7
6.2.4.8	6.2.4.9	6.2.5.1	6.2.5.2	6.2.5.3	6.2.5.4	6.2.5.5	6.2.5.6	6.2.5.7	6.2.5.8
6.2.5.9	6.2.6.1	6.2.6.2	6.2.6.3	6.2.6.4	6.2.6.5	6.2.6.6	6.2.6.7	6.2.6.8	6.2.6.9
6.2.7.1	6.2.7.2	6.2.7.3	6.2.7.4	6.2.7.5	6.2.7.6	6.2.7.7	6.2.7.8	6.2.7.9	6.2.8.1
6.2.8.2	6.2.8.3	6.2.8.4	6.2.8.5	6.2.8.6	6.2.8.7	6.2.8.8	6.2.8.9	6.2.9.1	6.2.9.2
6.2.9.3	6.2.9.4	6.2.9.5	6.2.9.6	6.2.9.7	6.2.9.8	6.2.9.9	6.3.1.1	6.3.1.2	6.3.1.3
6.3.1.4	6.3.1.5	6.3.1.6	6.3.1.7	6.3.1.8	6.3.1.9	6.3.2.1	6.3.2.2	6.3.2.3	6.3.2.4
6.3.2.5	6.3.2.6	6.3.2.7	6.3.2.8	6.3.2.9	6.3.3.1	6.3.3.2	6.3.3.3	6.3.3.4	6.3.3.5
6.3.3.6	6.3.3.7	6.3.3.8	6.3.3.9	6.3.4.1	6.3.4.2	6.3.4.3	6.3.4.4	6.3.4.5	6.3.4.6

Table 2- continued

6.3.4.7	6.3.4.8	6.3.4.9	6.3.5.1	6.3.5.2	6.3.5.3	6.3.5.4	6.3.5.5	6.3.5.6	6.3.5.7
6.3.5.8	6.3.5.9	6.3.6.1	6.3.6.2	6.3.6.3	6.3.6.4	6.3.6.5	6.3.6.6	6.3.6.7	6.3.6.8
6.3.6.9	6.3.7.1	6.3.7.2	6.3.7.3	6.3.7.4	6.3.7.5	6.3.7.6	6.3.7.7	6.3.7.8	6.3.7.9
6.3.8.1	6.3.8.2	6.3.8.3	6.3.8.4	6.3.8.5	6.3.8.6	6.3.8.7	6.3.8.8	6.3.8.9	6.3.9.1
6.3.9.2	6.3.9.3	6.3.9.4	6.3.9.5	6.3.9.6	6.3.9.7	6.3.9.8	6.3.9.9	6.4.1.1	6.4.1.2
6.4.1.3	6.4.1.4	6.4.1.5	6.4.1.6	6.4.1.7	6.4.1.8	6.4.1.9	6.4.2.1	6.4.2.2	6.4.2.3
6.4.2.4	6.4.2.5	6.4.2.6	6.4.2.7	6.4.2.8	6.4.2.9	6.4.3.1	6.4.3.2	6.4.3.3	6.4.3.4
6.4.3.5	6.4.3.6	6.4.3.7	6.4.3.8	6.4.3.9	6.4.4.1	6.4.4.2	6.4.4.3	6.4.4.4	6.4.4.5
6.4.4.6	6.4.4.7	6.4.4.8	6.4.4.9	6.4.5.1	6.4.5.2	6.4.5.3	6.4.5.4	6.4.5.5	6.4.5.6
6.4.5.7	6.4.5.8	6.4.5.9	6.4.6.1	6.4.6.2	6.4.6.3	6.4.6.4	6.4.6.5	6.4.6.6	6.4.6.7
6.4.6.8	6.4.6.9	6.4.7.1	6.4.7.2	6.4.7.3	6.4.7.4	6.4.7.5	6.4.7.6	6.4.7.7	6.4.7.8
6.4.7.9	6.4.8.1	6.4.8.2	6.4.8.3	6.4.8.4	6.4.8.5	6.4.8.6	6.4.8.7	6.4.8.8	6.4.8.9
6.4.9.1	6.4.9.2	6.4.9.3	6.4.9.4	6.4.9.5	6.4.9.6	6.4.9.7	6.4.9.8	6.4.9.9	6.5.1.1
6.5.1.2	6.5.1.3	6.5.1.4	6.5.1.5	6.5.1.6	6.5.1.7	6.5.1.8	6.5.1.9	6.5.2.1	6.5.2.2
6.5.2.3	6.5.2.4	6.5.2.5	6.5.2.6	6.5.2.7	6.5.2.8	6.5.2.9	6.5.3.1	6.5.3.2	6.5.3.3
6.5.3.4	6.5.3.5	6.5.3.6	6.5.3.7	6.5.3.8	6.5.3.9	6.5.4.1	6.5.4.2	6.5.4.3	6.5.4.4
6.5.4.5	6.5.4.6	6.5.4.7	6.5.4.8	6.5.4.9	6.5.5.1	6.5.5.2	6.5.5.3	6.5.5.4	6.5.5.5
6.5.5.6	6.5.5.7	6.5.5.8	6.5.5.9	6.5.6.1	6.5.6.2	6.5.6.3	6.5.6.4	6.5.6.5	6.5.6.6
6.5.6.7	6.5.6.8	6.5.6.9	6.5.7.1	6.5.7.2	6.5.7.3	6.5.7.4	6.5.7.5	6.5.7.6	6.5.7.7
6.5.7.8	6.5.7.9	6.5.8.1	6.5.8.2	6.5.8.3	6.5.8.4	6.5.8.5	6.5.8.6	6.5.8.7	6.5.8.8
6.5.8.9	6.5.9.1	6.5.9.2	6.5.9.3	6.5.9.4	6.5.9.5	6.5.9.6	6.5.9.7	6.5.9.8	6.5.9.9
6.6.1.1	6.6.1.2	6.6.1.3	6.6.1.4	6.6.1.5	6.6.1.6	6.6.1.7	6.6.1.8	6.6.1.9	6.6.2.1
6.6.2.2	6.6.2.3	6.6.2.4	6.6.2.5	6.6.2.6	6.6.2.7	6.6.2.8	6.6.2.9	6.6.3.1	6.6.3.2
6.6.3.3	6.6.3.4	6.6.3.5	6.6.3.6	6.6.3.7	6.6.3.8	6.6.3.9	6.6.4.1	6.6.4.2	6.6.4.3
6.6.4.4	6.6.4.5	6.6.4.6	6.6.4.7	6.6.4.8	6.6.4.9	6.6.5.1	6.6.5.2	6.6.5.3	6.6.5.4
6.6.5.5	6.6.5.6	6.6.5.7	6.6.5.8	6.6.5.9	6.6.6.1	6.6.6.2	6.6.6.3	6.6.6.4	6.6.6.5
6.6.6.6	6.6.6.7	6.6.6.8	6.6.6.9	6.6.7.1	6.6.7.2	6.6.7.3	6.6.7.4	6.6.7.5	6.6.7.6
6.6.7.7	6.6.7.8	6.6.7.9	6.6.8.1	6.6.8.2	6.6.8.3	6.6.8.4	6.6.8.5	6.6.8.6	6.6.8.7
6.6.8.8	6.6.8.9	6.6.9.1	6.6.9.2	6.6.9.3	6.6.9.4	6.6.9.5	6.6.9.6	6.6.9.7	6.6.9.8
6.6.9.9	6.7.1.1	6.7.1.2	6.7.1.3	6.7.1.4	6.7.1.5	6.7.1.6	6.7.1.7	6.7.1.8	6.7.1.9
6.7.2.1	6.7.2.2	6.7.2.3	6.7.2.4	6.7.2.5	6.7.2.6	6.7.2.7	6.7.2.8	6.7.2.9	6.7.3.1
6.7.3.2	6.7.3.3	6.7.3.4	6.7.3.5	6.7.3.6	6.7.3.7	6.7.3.8	6.7.3.9	6.7.4.1	6.7.4.2
6.7.4.3	6.7.4.4	6.7.4.5	6.7.4.6	6.7.4.7	6.7.4.8	6.7.4.9	6.7.5.1	6.7.5.2	6.7.5.3
6.7.5.4	6.7.5.5	6.7.5.6	6.7.5.7	6.7.5.8	6.7.5.9	6.7.6.1	6.7.6.2	6.7.6.3	6.7.6.4
6.7.6.5	6.7.6.6	6.7.6.7	6.7.6.8	6.7.6.9	6.7.7.1	6.7.7.2	6.7.7.3	6.7.7.4	6.7.7.5
6.7.7.6	6.7.7.7	6.7.7.8	6.7.7.9	6.7.8.1	6.7.8.2	6.7.8.3	6.7.8.4	6.7.8.5	6.7.8.6
6.7.8.7	6.7.8.8	6.7.8.9	6.7.9.1	6.7.9.2	6.7.9.3	6.7.9.4	6.7.9.5	6.7.9.6	6.7.9.7
6.7.9.8	6.7.9.9	6.8.1.1	6.8.1.2	6.8.1.3	6.8.1.4	6.8.1.5	6.8.1.6	6.8.1.7	6.8.1.8
6.8.1.9	6.8.2.1	6.8.2.2	6.8.2.3	6.8.2.4	6.8.2.5	6.8.2.6	6.8.2.7	6.8.2.8	6.8.2.9
6.8.3.1	6.8.3.2	6.8.3.3	6.8.3.4	6.8.3.5	6.8.3.6	6.8.3.7	6.8.3.8	6.8.3.9	6.8.4.1
6.8.4.2	6.8.4.3	6.8.4.4	6.8.4.5	6.8.4.6	6.8.4.7	6.8.4.8	6.8.4.9	6.8.5.1	6.8.5.2
6.8.5.3	6.8.5.4	6.8.5.5	6.8.5.6	6.8.5.7	6.8.5.8	6.8.5.9	6.8.6.1	6.8.6.2	6.8.6.3
6.8.6.4	6.8.6.5	6.8.6.6	6.8.6.7	6.8.6.8	6.8.6.9	6.8.7.1	6.8.7.2	6.8.7.3	6.8.7.4
6.8.7.5	6.8.7.6	6.8.7.7	6.8.7.8	6.8.7.9	6.8.8.1	6.8.8.2	6.8.8.3	6.8.8.4	6.8.8.5
6.8.8.6	6.8.8.7	6.8.8.8	6.8.8.9	6.8.9.1	6.8.9.2	6.8.9.3	6.8.9.4	6.8.9.5	6.8.9.6
6.8.9.7	6.8.9.8	6.8.9.9	6.9.1.1	6.9.1.2	6.9.1.3	6.9.1.4	6.9.1.5	6.9.1.6	6.9.1.7
6.9.1.8	6.9.1.9	6.9.2.1	6.9.2.2	6.9.2.3	6.9.2.4	6.9.2.5	6.9.2.6	6.9.2.7	6.9.2.8
6.9.2.9	6.9.3.1	6.9.3.2	6.9.3.3	6.9.3.4	6.9.3.5	6.9.3.6	6.9.3.7	6.9.3.8	6.9.3.9

Table 2 - continued

6.9.4.1	6.9.4.2	6.9.4.3	6.9.4.4	6.9.4.5	6.9.4.6	6.9.4.7	6.9.4.8	6.9.4.9	6.9.5.1
6.9.5.2	6.9.5.3	6.9.5.4	6.9.5.5	6.9.5.6	6.9.5.7	6.9.5.8	6.9.5.9	6.9.6.1	6.9.6.2
6.9.6.3	6.9.6.4	6.9.6.5	6.9.6.6	6.9.6.7	6.9.6.8	6.9.6.9	6.9.7.1	6.9.7.2	6.9.7.3
6.9.7.4	6.9.7.5	6.9.7.6	6.9.7.7	6.9.7.8	6.9.7.9	6.9.8.1	6.9.8.2	6.9.8.3	6.9.8.4
6.9.8.5	6.9.8.6	6.9.8.7	6.9.8.8	6.9.8.9	6.9.9.1	6.9.9.2	6.9.9.3	6.9.9.4	6.9.9.5
6.9.9.6	6.9.9.7	6.9.9.8	6.9.9.9	7.1.1.1	7.1.1.2	7.1.1.3	7.1.1.4	7.1.1.5	7.1.1.6
7.1.1.7	7.1.1.8	7.1.1.9	7.1.2.1	7.1.2.2	7.1.2.3	7.1.2.4	7.1.2.5	7.1.2.6	7.1.2.7
7.1.2.8	7.1.2.9	7.1.3.1	7.1.3.2	7.1.3.3	7.1.3.4	7.1.3.5	7.1.3.6	7.1.3.7	7.1.3.8
7.1.3.9	7.1.4.1	7.1.4.2	7.1.4.3	7.1.4.4	7.1.4.5	7.1.4.6	7.1.4.7	7.1.4.8	7.1.4.9
7.1.5.1	7.1.5.2	7.1.5.3	7.1.5.4	7.1.5.5	7.1.5.6	7.1.5.7	7.1.5.8	7.1.5.9	7.1.6.1
7.1.6.2	7.1.6.3	7.1.6.4	7.1.6.5	7.1.6.6	7.1.6.7	7.1.6.8	7.1.6.9	7.1.7.1	7.1.7.2
7.1.7.3	7.1.7.4	7.1.7.5	7.1.7.6	7.1.7.7	7.1.7.8	7.1.7.9	7.1.8.1	7.1.8.2	7.1.8.3
7.1.8.4	7.1.8.5	7.1.8.6	7.1.8.7	7.1.8.8	7.1.8.9	7.1.9.1	7.1.9.2	7.1.9.3	7.1.9.4
7.1.9.5	7.1.9.6	7.1.9.7	7.1.9.8	7.1.9.9	7.2.1.1	7.2.1.2	7.2.1.3	7.2.1.4	7.2.1.5
7.2.1.6	7.2.1.7	7.2.1.8	7.2.1.9	7.2.2.1	7.2.2.2	7.2.2.3	7.2.2.4	7.2.2.5	7.2.2.6
7.2.2.7	7.2.2.8	7.2.2.9	7.2.3.1	7.2.3.2	7.2.3.3	7.2.3.4	7.2.3.5	7.2.3.6	7.2.3.7
7.2.3.8	7.2.3.9	7.2.4.1	7.2.4.2	7.2.4.3	7.2.4.4	7.2.4.5	7.2.4.6	7.2.4.7	7.2.4.8
7.2.4.9	7.2.5.1	7.2.5.2	7.2.5.3	7.2.5.4	7.2.5.5	7.2.5.6	7.2.5.7	7.2.5.8	7.2.5.9
7.2.6.1	7.2.6.2	7.2.6.3	7.2.6.4	7.2.6.5	7.2.6.6	7.2.6.7	7.2.6.8	7.2.6.9	7.2.7.1
7.2.7.2	7.2.7.3	7.2.7.4	7.2.7.5	7.2.7.6	7.2.7.7	7.2.7.8	7.2.7.9	7.2.8.1	7.2.8.2
7.2.8.3	7.2.8.4	7.2.8.5	7.2.8.6	7.2.8.7	7.2.8.8	7.2.8.9	7.2.9.1	7.2.9.2	7.2.9.3
7.2.9.4	7.2.9.5	7.2.9.6	7.2.9.7	7.2.9.8	7.2.9.9	7.3.1.1	7.3.1.2	7.3.1.3	7.3.1.4
7.3.1.5	7.3.1.6	7.3.1.7	7.3.1.8	7.3.1.9	7.3.2.1	7.3.2.2	7.3.2.3	7.3.2.4	7.3.2.5
7.3.2.6	7.3.2.7	7.3.2.8	7.3.2.9	7.3.3.1	7.3.3.2	7.3.3.3	7.3.3.4	7.3.3.5	7.3.3.6
7.3.3.7	7.3.3.8	7.3.3.9	7.3.4.1	7.3.4.2	7.3.4.3	7.3.4.4	7.3.4.5	7.3.4.6	7.3.4.7
7.3.4.8	7.3.4.9	7.3.5.1	7.3.5.2	7.3.5.3	7.3.5.4	7.3.5.5	7.3.5.6	7.3.5.7	7.3.5.8
7.3.5.9	7.3.6.1	7.3.6.2	7.3.6.3	7.3.6.4	7.3.6.5	7.3.6.6	7.3.6.7	7.3.6.8	7.3.6.9
7.3.7.1	7.3.7.2	7.3.7.3	7.3.7.4	7.3.7.5	7.3.7.6	7.3.7.7	7.3.7.8	7.3.7.9	7.3.8.1
7.3.8.2	7.3.8.3	7.3.8.4	7.3.8.5	7.3.8.6	7.3.8.7	7.3.8.8	7.3.8.9	7.3.9.1	7.3.9.2
7.3.9.3	7.3.9.4	7.3.9.5	7.3.9.6	7.3.9.7	7.3.9.8	7.3.9.9	7.4.1.1	7.4.1.2	7.4.1.3
7.4.1.4	7.4.1.5	7.4.1.6	7.4.1.7	7.4.1.8	7.4.1.9	7.4.2.1	7.4.2.2	7.4.2.3	7.4.2.4
7.4.2.5	7.4.2.6	7.4.2.7	7.4.2.8	7.4.2.9	7.4.3.1	7.4.3.2	7.4.3.3	7.4.3.4	7.4.3.5
7.4.3.6	7.4.3.7	7.4.3.8	7.4.3.9	7.4.4.1	7.4.4.2	7.4.4.3	7.4.4.4	7.4.4.5	7.4.4.6
7.4.4.7	7.4.4.8	7.4.4.9	7.4.5.1	7.4.5.2	7.4.5.3	7.4.5.4	7.4.5.5	7.4.5.6	7.4.5.7
7.4.5.8	7.4.5.9	7.4.6.1	7.4.6.2	7.4.6.3	7.4.6.4	7.4.6.5	7.4.6.6	7.4.6.7	7.4.6.8
7.4.6.9	7.4.7.1	7.4.7.2	7.4.7.3	7.4.7.4	7.4.7.5	7.4.7.6	7.4.7.7	7.4.7.8	7.4.7.9
7.4.8.1	7.4.8.2	7.4.8.3	7.4.8.4	7.4.8.5	7.4.8.6	7.4.8.7	7.4.8.8	7.4.8.9	7.4.9.1
7.4.9.2	7.4.9.3	7.4.9.4	7.4.9.5	7.4.9.6	7.4.9.7	7.4.9.8	7.4.9.9	7.5.1.1	7.5.1.2
7.5.1.3	7.5.1.4	7.5.1.5	7.5.1.6	7.5.1.7	7.5.1.8	7.5.1.9	7.5.2.1	7.5.2.2	7.5.2.3
7.5.2.4	7.5.2.5	7.5.2.6	7.5.2.7	7.5.2.8	7.5.2.9	7.5.3.1	7.5.3.2	7.5.3.3	7.5.3.4
7.5.3.5	7.5.3.6	7.5.3.7	7.5.3.8	7.5.3.9	7.5.4.1	7.5.4.2	7.5.4.3	7.5.4.4	7.5.4.5
7.5.4.6	7.5.4.7	7.5.4.8	7.5.4.9	7.5.5.1	7.5.5.2	7.5.5.3	7.5.5.4	7.5.5.5	7.5.5.6
7.5.5.7	7.5.5.8	7.5.5.9	7.5.6.1	7.5.6.2	7.5.6.3	7.5.6.4	7.5.6.5	7.5.6.6	7.5.6.7
7.5.6.8	7.5.6.9	7.5.7.1	7.5.7.2	7.5.7.3	7.5.7.4	7.5.7.5	7.5.7.6	7.5.7.7	7.5.7.8
7.5.7.9	7.5.8.1	7.5.8.2	7.5.8.3	7.5.8.4	7.5.8.5	7.5.8.6	7.5.8.7	7.5.8.8	7.5.8.9
7.5.9.1	7.5.9.2	7.5.9.3	7.5.9.4	7.5.9.5	7.5.9.6	7.5.9.7	7.5.9.8	7.5.9.9	7.6.1.1
7.6.1.2	7.6.1.3	7.6.1.4	7.6.1.5	7.6.1.6	7.6.1.7	7.6.1.8	7.6.1.9	7.6.2.1	7.6.2.2
7.6.2.3	7.6.2.4	7.6.2.5	7.6.2.6	7.6.2.7	7.6.2.8	7.6.2.9	7.6.3.1	7.6.3.2	7.6.3.3

Table 2 - continued

7.6.3.4	7.6.3.5	7.6.3.6	7.6.3.7	7.6.3.8	7.6.3.9	7.6.4.1	7.6.4.2	7.6.4.3	7.6.4.4
7.6.4.5	7.6.4.6	7.6.4.7	7.6.4.8	7.6.4.9	7.6.5.1	7.6.5.2	7.6.5.3	7.6.5.4	7.6.5.5
7.6.5.6	7.6.5.7	7.6.5.8	7.6.5.9	7.6.6.1	7.6.6.2	7.6.6.3	7.6.6.4	7.6.6.5	7.6.6.6
7.6.6.7	7.6.6.8	7.6.6.9	7.6.7.1	7.6.7.2	7.6.7.3	7.6.7.4	7.6.7.5	7.6.7.6	7.6.7.7
7.6.7.8	7.6.7.9	7.6.8.1	7.6.8.2	7.6.8.3	7.6.8.4	7.6.8.5	7.6.8.6	7.6.8.7	7.6.8.8
7.6.8.9	7.6.9.1	7.6.9.2	7.6.9.3	7.6.9.4	7.6.9.5	7.6.9.6	7.6.9.7	7.6.9.8	7.6.9.9
7.7.1.1	7.7.1.2	7.7.1.3	7.7.1.4	7.7.1.5	7.7.1.6	7.7.1.7	7.7.1.8	7.7.1.9	7.7.2.1
7.7.2.2	7.7.2.3	7.7.2.4	7.7.2.5	7.7.2.6	7.7.2.7	7.7.2.B	7.7.2.9	7.7.3.1	
7.7.3.2									
7.7.3.3	7.7.3.4	7.7.3.5	7.7.3.6	7.7.3.7	7.7.3.8	7.7.3.9	7.7.4.1	7.7.4.2	7.7.4.3
7.7.4.4	7.7.4.5	7.7.4.6	7.7.4.7	7.7.4.8	7.7.4.9	7.7.5.1	7.7.5.2	7.7.5.3	7.7.5.4
7.7.5.5	7.7.5.6	7.7.5.7	7.7.5.8	7.7.5.9	7.7.6.1	7.7.6.2	7.7.6.3	7.7.6.4	7.7.6.5
7.7.6.6	7.7.6.7	7.7.6.8	7.7.6.9	7.7.7.1	7.7.7.2	7.7.7.3	7.7.7.4	7.7.7.5	7.7.7.6
7.7.7.7	7.7.7.8	7.7.7.9	7.7.8.1	7.7.8.2	7.7.8.3	7.7.8.4	7.7.8.5	7.7.8.6	7.7.8.7
7.7.8.8	7.7.8.9	7.7.9.1	7.7.9.2	7.7.9.3	7.7.9.4	7.7.9.5	7.7.9.6	7.7.9.7	7.7.9.8
7.7.9.9	7.8.1.1	7.8.1.2	7.8.1.3	7.8.1.4	7.8.1.5	7.8.1.6	7.8.1.7	7.8.1.8	7.8.1.9
7.8.2.1	7.8.2.2	7.8.2.3	7.8.2.4	7.8.2.5	7.8.2.6	7.8.2.7	7.8.2.8	7.8.2.9	7.8.3.1
7.8.3.2	7.8.3.3	7.8.3.4	7.8.3.5	7.8.3.6	7.8.3.7	7.8.3.8	7.8.3.9	7.8.4.1	7.8.4.2
7.8.4.3	7.8.4.4	7.8.4.5	7.8.4.6	7.8.4.7	7.8.4.8	7.8.4.9	7.8.5.1	7.8.5.2	7.8.5.3
7.8.5.4	7.8.5.5	7.8.5.6	7.8.5.7	7.8.5.8	7.8.5.9	7.8.6.1	7.8.6.2	7.8.6.3	7.8.6.4
7.8.6.5	7.8.6.6	7.8.6.7	7.8.6.8	7.8.6.9	7.8.7.1	7.8.7.2	7.8.7.3	7.8.7.4	7.8.7.5
7.8.7.6	7.8.7.7	7.8.7.8	7.8.7.9	7.8.8.1	7.8.8.2	7.8.8.3	7.8.8.4	7.8.8.5	7.8.8.6
7.8.8.7	7.8.8.8	7.8.8.9	7.8.9.1	7.8.9.2	7.8.9.3	7.8.9.4	7.8.9.5	7.8.9.6	7.8.9.7
7.8.9.8	7.8.9.9	7.9.1.1	7.9.1.2	7.9.1.3	7.9.1.4	7.9.1.5	7.9.1.6	7.9.1.7	7.9.1.8
7.9.1.9	7.9.2.1	7.9.2.2	7.9.2.3	7.9.2.4	7.9.2.5	7.9.2.6	7.9.2.7	7.9.2.8	7.9.2.9
7.9.3.1	7.9.3.2	7.9.3.3	7.9.3.4	7.9.3.5	7.9.3.6	7.9.3.7	7.9.3.8	7.9.3.9	7.9.4.1
7.9.4.2	7.9.4.3	7.9.4.4	7.9.4.5	7.9.4.6	7.9.4.7	7.9.4.8	7.9.4.9	7.9.5.1	7.9.5.2
7.9.5.3	7.9.5.4	7.9.5.5	7.9.5.6	7.9.5.7	7.9.5.8	7.9.5.9	7.9.6.1	7.9.6.2	7.9.6.3
7.9.6.4	7.9.6.5	7.9.6.6	7.9.6.7	7.9.6.8	7.9.6.9	7.9.7.1	7.9.7.2	7.9.7.3	7.9.7.4
7.9.7.5	7.9.7.6	7.9.7.7	7.9.7.8	7.9.7.9	7.9.8.1	7.9.8.2	7.9.8.3	7.9.8.4	7.9.8.5
7.9.8.6	7.9.8.7	7.9.8.8	7.9.8.9	7.9.9.1	7.9.9.2	7.9.9.3	7.9.9.4	7.9.9.5	7.9.9.6
7.9.9.7	7.9.9.8	7.9.9.9	8.1.1.1	8.1.1.2	8.1.1.3	8.1.1.4	8.1.1.5	8.1.1.6	8.1.1.7
8.1.1.8	8.1.1.9	8.1.2.1	8.1.2.2	8.1.2.3	8.1.2.4	8.1.2.5	8.1.2.6	8.1.2.7	8.1.2.8
8.1.2.9	8.1.3.1	8.1.3.2	8.1.3.3	8.1.3.4	8.1.3.5	8.1.3.6	8.1.3.7	8.1.3.8	8.1.3.9
8.1.4.1	8.1.4.2	8.1.4.3	8.1.4.4	8.1.4.5	8.1.4.6	8.1.4.7	8.1.4.8	8.1.4.9	8.1.5.1
8.1.5.2	8.1.5.3	8.1.5.4	8.1.5.5	8.1.5.6	8.1.5.7	8.1.5.8	8.1.5.9	8.1.6.1	8.1.6.2
8.1.6.3	8.1.6.4	8.1.6.5	8.1.6.6	8.1.6.7	8.1.6.8	8.1.6.9	8.1.7.1	8.1.7.2	8.1.7.3
8.1.7.4	8.1.7.5	8.1.7.6	8.1.7.7	8.1.7.8	8.1.7.9	8.1.8.1	8.1.8.2	8.1.8.3	8.1.8.4
8.1.8.5	8.1.8.6	8.1.8.7	8.1.8.8	8.1.8.9	8.1.9.1	8.1.9.2	8.1.9.3	8.1.9.4	8.1.9.5
8.1.9.6	8.1.9.7	8.1.9.8	8.1.9.9	8.2.1.1	8.2.1.2	8.2.1.3	8.2.1.4	8.2.1.5	8.2.1.6
8.2.1.7	8.2.1.8	8.2.1.9	8.2.2.1	8.2.2.2	8.2.2.3	8.2.2.4	8.2.2.5	8.2.2.6	8.2.2.7
8.2.2.8	8.2.2.9	8.2.3.1	8.2.3.2	8.2.3.3	8.2.3.4	8.2.3.5	8.2.3.6	8.2.3.7	8.2.3.8
8.2.3.9	8.2.4.1	8.2.4.2	8.2.4.3	8.2.4.4	8.2.4.5	8.2.4.6	8.2.4.7	8.2.4.8	8.2.4.9
8.2.5.1	8.2.5.2	8.2.5.3	8.2.5.4	8.2.5.5	8.2.5.6	8.2.5.7	8.2.5.8	8.2.5.9	8.2.6.1
8.2.6.2	8.2.6.3	8.2.6.4	8.2.6.5	8.2.6.6	8.2.6.7	8.2.6.8	8.2.6.9	8.2.7.1	8.2.7.2
8.2.7.3	8.2.7.4	8.2.7.5	8.2.7.6	8.2.7.7	8.2.7.8	8.2.7.9	8.2.8.1	8.2.8.2	8.2.8.3
8.2.8.4	8.2.8.5	8.2.8.6	8.2.8.7	8.2.8.8	8.2.8.9	8.2.9.1	8.2.9.2	8.2.9.3	8.2.9.4
8.2.9.5	8.2.9.6	8.2.9.7	8.2.9.8	8.2.9.9	8.3.1.1	8.3.1.2	8.3.1.3	8.3.1.4	8.3.1.5
8.3.1.6	8.3.1.7	8.3.1.8	8.3.1.9	8.3.2.1	8.3.2.2	8.3.2.3	8.3.2.4	8.3.2.5	8.3.2.6

Table 2- continued

8.3.2.7	8.3.2.8	8.3.2.9	8.3.3.1	8.3.3.2	8.3.3.3	8.3.3.4	8.3.3.5	8.3.3.6	8.3.3.7
8.3.3.8	8.3.3.9	8.3.4.1	8.3.4.2	8.3.4.3	8.3.4.4	8.3.4.5	8.3.4.6	8.3.4.7	8.3.4.8
8.3.4.9	8.3.5.1	8.3.5.2	8.3.5.3	8.3.5.4	8.3.5.5	8.3.5.6	8.3.5.7	8.3.5.8	8.3.5.9
8.3.6.1	8.3.6.2	8.3.6.3	8.3.6.4	8.3.6.5	8.3.6.6	8.3.6.7	8.3.6.8	8.3.6.9	8.3.7.1
8.3.7.2	8.3.7.3	8.3.7.4	8.3.7.5	8.3.7.6	8.3.7.7	8.3.7.8	8.3.7.9	8.3.8.1	8.3.8.2
8.3.8.3	8.3.8.4	8.3.8.5	8.3.8.6	8.3.8.7	8.3.8.8	8.3.8.9	8.3.9.1	8.3.9.2	8.3.9.3
8.3.9.4	8.3.9.5	8.3.9.6	8.3.9.7	8.3.9.8	8.3.9.9	8.4.1.1	8.4.1.2	8.4.1.3	8.4.1.4
8.4.1.5	8.4.1.6	8.4.1.7	8.4.1.8	8.4.1.9	8.4.2.1	8.4.2.2	8.4.2.3	8.4.2.4	8.4.2.5
8.4.2.6	8.4.2.7	8.4.2.8	8.4.2.9	8.4.3.1	8.4.3.2	8.4.3.3	8.4.3.4	8.4.3.5	8.4.3.6
8.4.3.7	8.4.3.8	8.4.3.9	8.4.4.1	8.4.4.2	8.4.4.3	8.4.4.4	8.4.4.5	8.4.4.6	8.4.4.7
8.4.4.8	8.4.4.9	8.4.5.1	8.4.5.2	8.4.5.3	8.4.5.4	8.4.5.5	8.4.5.6	8.4.5.7	8.4.5.8
8.4.5.9	8.4.6.1	8.4.6.2	8.4.6.3	8.4.6.4	8.4.6.5	8.4.6.6	8.4.6.7	8.4.6.8	8.4.6.9
8.4.7.1	8.4.7.2	8.4.7.3	8.4.7.4	8.4.7.5	8.4.7.6	8.4.7.7	8.4.7.8	8.4.7.9	8.4.8.1
8.4.8.2	8.4.8.3	8.4.8.4	8.4.8.5	8.4.8.6	8.4.8.7	8.4.8.8	8.4.8.9	8.4.9.1	8.4.9.2
8.4.9.3	8.4.9.4	8.4.9.5	8.4.9.6	8.4.9.7	8.4.9.8	8.4.9.9	8.5.1.1	8.5.1.2	8.5.1.3
8.5.1.4	8.5.1.5	8.5.1.6	8.5.1.7	8.5.1.8	8.5.1.9	8.5.2.1	8.5.2.2	8.5.2.3	8.5.2.4
8.5.2.5	8.5.2.6	8.5.2.7	8.5.2.8	8.5.2.9	8.5.3.1	8.5.3.2	8.5.3.3	8.5.3.4	8.5.3.5
8.5.3.6	8.5.3.7	8.5.3.8	8.5.3.9	8.5.4.1	8.5.4.2	8.5.4.3	8.5.4.4	8.5.4.5	8.5.4.6
8.5.4.7	8.5.4.8	8.5.4.9	8.5.5.1	8.5.5.2	8.5.5.3	8.5.5.4	8.5.5.5	8.5.5.6	8.5.5.7
8.5.5.8	8.5.5.9	8.5.6.1	8.5.6.2	8.5.6.3	8.5.6.4	8.5.6.5	8.5.6.6	8.5.6.7	8.5.6.8
8.5.6.9	8.5.7.1	8.5.7.2	8.5.7.3	8.5.7.4	8.5.7.5	8.5.7.6	8.5.7.7	8.5.7.8	8.5.7.9
8.5.8.1	8.5.8.2	8.5.8.3	8.5.8.4	8.5.8.5	8.5.8.6	8.5.8.7	8.5.8.8	8.5.8.9	8.5.9.1
8.5.9.2	8.5.9.3	8.5.9.4	8.5.9.5	8.5.9.6	8.5.9.7	8.5.9.8	8.5.9.9	8.6.1.1	8.6.1.2
8.6.1.3	8.6.1.4	8.6.1.5	8.6.1.6	8.6.1.7	8.6.1.8	8.6.1.9	8.6.2.1	8.6.2.2	8.6.2.3
8.6.2.4	8.6.2.5	8.6.2.6	8.6.2.7	8.6.2.8	8.6.2.9	8.6.3.1	8.6.3.2	8.6.3.3	8.6.3.4
8.6.3.5	8.6.3.6	8.6.3.7	8.6.3.8	8.6.3.9	8.6.4.1	8.6.4.2	8.6.4.3	8.6.4.4	8.6.4.5
8.6.4.6	8.6.4.7	8.6.4.8	8.6.4.9	8.6.5.1	8.6.5.2	8.6.5.3	8.6.5.4	8.6.5.5	8.6.5.6
8.6.5.7	8.6.5.8	8.6.5.9	8.6.6.1	8.6.6.2	8.6.6.3	8.6.6.4	8.6.6.5	8.6.6.6	8.6.6.7
8.6.6.8	8.6.6.9	8.6.7.1	8.6.7.2	8.6.7.3	8.6.7.4	8.6.7.5	8.6.7.6	8.6.7.7	8.6.7.8
8.6.7.9	8.6.8.1	8.6.8.2	8.6.8.3	8.6.8.4	8.6.8.5	8.6.8.6	8.6.8.7	8.6.8.8	8.6.8.9
8.6.9.1	8.6.9.2	8.6.9.3	8.6.9.4	8.6.9.5	8.6.9.6	8.6.9.7	8.6.9.8	8.6.9.9	8.7.1.1
8.7.1.2	8.7.1.3	8.7.1.4	8.7.1.5	8.7.1.6	8.7.1.7	8.7.1.8	8.7.1.9	8.7.2.1	8.7.2.2
8.7.2.3	8.7.2.4	8.7.2.5	8.7.2.6	8.7.2.7	8.7.2.8	8.7.2.9	8.7.3.1	8.7.3.2	8.7.3.3
8.7.3.4	8.7.3.5	8.7.3.6	8.7.3.7	8.7.3.8	8.7.3.9	8.7.4.1	8.7.4.2	8.7.4.3	8.7.4.4
8.7.4.5	8.7.4.6	8.7.4.7	8.7.4.8	8.7.4.9	8.7.5.1	8.7.5.2	8.7.5.3	8.7.5.4	8.7.5.5
8.7.5.6	8.7.5.7	8.7.5.8	8.7.5.9	8.7.6.1	8.7.6.2	8.7.6.3	8.7.6.4	8.7.6.5	8.7.6.6
8.7.6.7	8.7.6.8	8.7.6.9	8.7.7.1	8.7.7.2	8.7.7.3	8.7.7.4	8.7.7.5	8.7.7.6	8.7.7.7
8.7.7.8	8.7.7.9	8.7.8.1	8.7.8.2	8.7.8.3	8.7.8.4	8.7.8.5	8.7.8.6	8.7.8.7	8.7.8.8
8.7.8.9	8.7.9.1	8.7.9.2	8.7.9.3	8.7.9.4	8.7.9.5	8.7.9.6	8.7.9.7	8.7.9.8	8.7.9.9
8.8.1.1	8.8.1.2	8.8.1.3	8.8.1.4	8.8.1.5	8.8.1.6	8.8.1.7	8.8.1.8	8.8.1.9	8.8.2.1
8.8.2.2	8.8.2.3	8.8.2.4	8.8.2.5	8.8.2.6	8.8.2.7	8.8.2.8	8.8.2.9	8.8.3.1	8.8.3.2
8.8.3.3	8.8.3.4	8.8.3.5	8.8.3.6	8.8.3.7	8.8.3.8	8.8.3.9	8.8.4.1	8.8.4.2	8.8.4.3
8.8.4.4	8.8.4.5	8.8.4.6	8.8.4.7	8.8.4.8	8.8.4.9	8.8.5.1	8.8.5.2	8.8.5.3	8.8.5.4
8.8.5.5	8.8.5.6	8.8.5.7	8.8.5.8	8.8.5.9	8.8.6.1	8.8.6.2	8.8.6.3	8.8.6.4	8.8.6.5
8.8.6.6	8.8.6.7	8.8.6.8	8.8.6.9	8.8.7.1	8.8.7.2	8.8.7.3	8.8.7.4	8.8.7.5	8.8.7.6
8.8.7.7	8.8.7.8	8.8.7.9	8.8.8.1	8.8.8.2	8.8.8.3	8.8.8.4	8.8.8.5	8.8.8.6	8.8.8.7
8.8.8.8	8.8.8.9	8.8.9.1	8.8.9.2	8.8.9.3	8.8.9.4	8.8.9.5	8.8.9.6	8.8.9.7	8.8.9.8
8.8.9.9	8.9.1.1	8.9.1.2	8.9.1.3	8.9.1.4	8.9.1.5	8.9.1.6	8.9.1.7	8.9.1.8	8.9.1.9

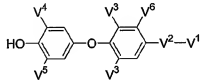
Table 2 - continued

8.9.2.1	8.9.2.2	8.9.2.3	8.9.2.4	8.9.2.5	8.9.2.6	8.9.2.7	8.9.2.8	8.9.2.9	8.9.3.1
8.9.3.2	8.9.3.3	8.9.3.4	8.9.3.5	8.9.3.6	8.9.3.7	8.9.3.8	8.9.3.9	8.9.4.1	8.9.4.2
8.9.4.3	8.9.4.4	8.9.4.5	8.9.4.6	8.9.4.7	8.9.4.8	8.9.4.9	8.9.5.1	8.9.5.2	8.9.5.3
8.9.5.4	8.9.5.5	8.9.5.6	8.9.5.7	8.9.5.8	8.9.5.9	8.9.6.1	8.9.6.2	8.9.6.3	8.9.6.4
8.9.6.5	8.9.6.6	8.9.6.7	8.9.6.8	8.9.6.9	8.9.7.1	8.9.7.2	8.9.7.3	8.9.7.4	8.9.7.5
8.9.7.6	8.9.7.7	8.9.7.8	8.9.7.9	8.9.8.1	8.9.8.2	8.9.8.3	8.9.8.4	8.9.8.5	8.9.8.6
8.9.8.7	8.9.8.8	8.9.8.9	8.9.9.1	8.9.9.2	8.9.9.3	8.9.9.4	8.9.9.5	8.9.9.6	8.9.9.7
8.9.9.8	8.9.9.9	9.1.1.1	9.1.1.2	9.1.1.3	9.1.1.4	9.1.1.5	9.1.1.6	9.1.1.7	9.1.1.8
9.1.1.9	9.1.2.1	9.1.2.2	9.1.2.3	9.1.2.4	9.1.2.5	9.1.2.6	9.1.2.7	9.1.2.8	9.1.2.9
9.1.3.1	9.1.3.2	9.1.3.3	9.1.3.4	9.1.3.5	9.1.3.6	9.1.3.7	9.1.3.8	9.1.3.9	9.1.4.1
9.1.4.2	9.1.4.3	9.1.4.4	9.1.4.5	9.1.4.6	9.1.4.7	9.1.4.8	9.1.4.9	9.1.5.1	9.1.5.2
9.1.5.3	9.1.5.4	9.1.5.5	9.1.5.6	9.1.5.7	9.1.5.8	9.1.5.9	9.1.6.1	9.1.6.2	9.1.6.3
9.1.6.4	9.1.6.5	9.1.6.6	9.1.6.7	9.1.6.8	9.1.6.9	9.1.7.1	9.1.7.2	9.1.7.3	9.1.7.4
9.1.7.5	9.1.7.6	9.1.7.7	9.1.7.8	9.1.7.9	9.1.8.1	9.1.8.2	9.1.8.3	9.1.8.4	9.1.8.5
9.1.8.6	9.1.8.7	9.1.8.8	9.1.8.9	9.1.9.1	9.1.9.2	9.1.9.3	9.1.9.4	9.1.9.5	9.1.9.6
9.1.9.7	9.1.9.8	9.1.9.9	9.2.1.1	9.2.1.2	9.2.1.3	9.2.1.4	9.2.1.5	9.2.1.6	9.2.1.7
9.2.1.8	9.2.1.9	9.2.2.1	9.2.2.2	9.2.2.3	9.2.2.4	9.2.2.5	9.2.2.6	9.2.2.7	9.2.2.8
9.2.2.9	9.2.3.1	9.2.3.2	9.2.3.3	9.2.3.4	9.2.3.5	9.2.3.6	9.2.3.7	9.2.3.8	9.2.3.9
9.2.4.1	9.2.4.2	9.2.4.3	9.2.4.4	9.2.4.5	9.2.4.6	9.2.4.7	9.2.4.8	9.2.4.9	9.2.5.1
9.2.5.2	9.2.5.3	9.2.5.4	9.2.5.5	9.2.5.6	9.2.5.7	9.2.5.8	9.2.5.9	9.2.6.1	9.2.6.2
9.2.6.3	9.2.6.4	9.2.6.5	9.2.6.6	9.2.6.7	9.2.6.8	9.2.6.9	9.2.7.1	9.2.7.2	9.2.7.3
9.2.7.4	9.2.7.5	9.2.7.6	9.2.7.7	9.2.7.8	9.2.7.9	9.2.8.1	9.2.8.2	9.2.8.3	9.2.8.4
9.2.8.5	9.2.8.6	9.2.8.7	9.2.8.8	9.2.8.9	9.2.9.1	9.2.9.2	9.2.9.3	9.2.9.4	9.2.9.5
9.2.9.6	9.2.9.7	9.2.9.8	9.2.9.9	9.3.1.1	9.3.1.2	9.3.1.3	9.3.1.4	9.3.1.5	9.3.1.6
9.3.1.7	9.3.1.8	9.3.1.9	9.3.2.1	9.3.2.2	9.3.2.3	9.3.2.4	9.3.2.5	9.3.2.6	9.3.2.7
9.3.2.8	9.3.2.9	9.3.3.1	9.3.3.2	9.3.3.3	9.3.3.4	9.3.3.5	9.3.3.6	9.3.3.7	9.3.3.8
9.3.3.9	9.3.4.1	9.3.4.2	9.3.4.3	9.3.4.4	9.3.4.5	9.3.4.6	9.3.4.7	9.3.4.8	9.3.4.9
9.3.5.1	9.3.5.2	9.3.5.3	9.3.5.4	9.3.5.5	9.3.5.6	9.3.5.7	9.3.5.8	9.3.5.9	9.3.6.1
9.3.6.2	9.3.6.3	9.3.6.4	9.3.6.5	9.3.6.6	9.3.6.7	9.3.6.8	9.3.6.9	9.3.7.1	9.3.7.2
9.3.7.3	9.3.7.4	9.3.7.5	9.3.7.6	9.3.7.7	9.3.7.8	9.3.7.9	9.3.8.1	9.3.8.2	9.3.8.3
9.3.8.4	9.3.8.5	9.3.8.6	9.3.8.7	9.3.8.8	9.3.8.9	9.3.9.1	9.3.9.2	9.3.9.3	9.3.9.4
9.3.9.5	9.3.9.6	9.3.9.7	9.3.9.8	9.3.9.9	9.4.1.1	9.4.1.2	9.4.1.3	9.4.1.4	9.4.1.5
9.4.1.6	9.4.1.7	9.4.1.8	9.4.1.9	9.4.2.1	9.4.2.2	9.4.2.3	9.4.2.4	9.4.2.5	9.4.2.6
9.4.2.7	9.4.2.8	9.4.2.9	9.4.3.1	9.4.3.2	9.4.3.3	9.4.3.4	9.4.3.5	9.4.3.6	9.4.3.7
9.4.3.8	9.4.3.9	9.4.4.1	9.4.4.2	9.4.4.3	9.4.4.4	9.4.4.5	9.4.4.6	9.4.4.7	9.4.4.8
9.4.4.9	9.4.5.1	9.4.5.2	9.4.5.3	9.4.5.4	9.4.5.5	9.4.5.6	9.4.5.7	9.4.5.8	9.4.5.9
9.4.6.1	9.4.6.2	9.4.6.3	9.4.6.4	9.4.6.5	9.4.6.6	9.4.6.7	9.4.6.8	9.4.6.9	9.4.7.1
9.4.7.2	9.4.7.3	9.4.7.4	9.4.7.5	9.4.7.6	9.4.7.7	9.4.7.8	9.4.7.9	9.4.8.1	9.4.8.2
9.4.8.3	9.4.8.4	9.4.8.5	9.4.8.6	9.4.8.7	9.4.8.8	9.4.8.9	9.4.9.1	9.4.9.2	9.4.9.3
9.4.9.4	9.4.9.5	9.4.9.6	9.4.9.7	9.4.9.8	9.4.9.9	9.5.1.1	9.5.1.2	9.5.1.3	9.5.1.4
9.5.1.5	9.5.1.6	9.5.1.7	9.5.1.8	9.5.1.9	9.5.2.1	9.5.2.2	9.5.2.3	9.5.2.4	9.5.2.5
9.5.2.6	9.5.2.7	9.5.2.8	9.5.2.9	9.5.3.1	9.5.3.2	9.5.3.3	9.5.3.4	9.5.3.5	9.5.3.6
9.5.3.7	9.5.3.8	9.5.3.9	9.5.4.1	9.5.4.2	9.5.4.3	9.5.4.4	9.5.4.5	9.5.4.6	9.5.4.7
9.5.4.8	9.5.4.9	9.5.5.1	9.5.5.2	9.5.5.3	9.5.5.4	9.5.5.5	9.5.5.6	9.5.5.7	9.5.5.8
9.5.5.9	9.5.6.1	9.5.6.2	9.5.6.3	9.5.6.4	9.5.6.5	9.5.6.6	9.5.6.7	9.5.6.8	9.5.6.9
9.5.7.1	9.5.7.2	9.5.7.3	9.5.7.4	9.5.7.5	9.5.7.6	9.5.7.7	9.5.7.8	9.5.7.9	9.5.8.1
9.5.8.2	9.5.8.3	9.5.8.4	9.5.8.5	9.5.8.6	9.5.8.7	9.5.8.8	9.5.8.9	9.5.9.1	9.5.9.2
9.5.9.3	9.5.9.4	9.5.9.5	9.5.9.6	9.5.9.7	9.5.9.8	9.5.9.9	9.6.1.1	9.6.1.2	9.6.1.3

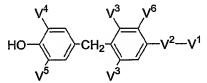
Table 2 - continued

9.6.1.4	9.6.1.5	9.6.1.6	9.6.1.7	9.6.1.8	9.6.1.9	9.6.2.1	9.6.2.2	9.6.2.3	9.6.2.4
9.6.2.5	9.6.2.6	9.6.2.7	9.6.2.8	9.6.2.9	9.6.3.1	9.6.3.2	9.6.3.3	9.6.3.4	9.6.3.5
9.6.3.6	9.6.3.7	9.6.3.8	9.6.3.9	9.6.4.1	9.6.4.2	9.6.4.3	9.6.4.4	9.6.4.5	9.6.4.6
9.6.4.7	9.6.4.8	9.6.4.9	9.6.5.1	9.6.5.2	9.6.5.3	9.6.5.4	9.6.5.5	9.6.5.6	9.6.5.7
9.6.5.8	9.6.5.9	9.6.6.1	9.6.6.2	9.6.6.3	9.6.6.4	9.6.6.5	9.6.6.6	9.6.6.7	9.6.6.8
9.6.6.9	9.6.7.1	9.6.7.2	9.6.7.3	9.6.7.4	9.6.7.5	9.6.7.6	9.6.7.7	9.6.7.8	9.6.7.9
9.6.8.1	9.6.8.2	9.6.8.3	9.6.8.4	9.6.8.5	9.6.8.6	9.6.8.7	9.6.8.8	9.6.8.9	9.6.9.1
9.6.9.2	9.6.9.3	9.6.9.4	9.6.9.5	9.6.9.6	9.6.9.7	9.6.9.8	9.6.9.9	9.7.1.1	9.7.1.2
9.7.1.3	9.7.1.4	9.7.1.5	9.7.1.6	9.7.1.7	9.7.1.8	9.7.1.9	9.7.2.1	9.7.2.2	9.7.2.3
9.7.2.4	9.7.2.5	9.7.2.6	9.7.2.7	9.7.2.8	9.7.2.9	9.7.3.1	9.7.3.2	9.7.3.3	9.7.3.4
9.7.3.5	9.7.3.6	9.7.3.7	9.7.3.8	9.7.3.9	9.7.4.1	9.7.4.2	9.7.4.3	9.7.4.4	9.7.4.5
9.7.4.6	9.7.4.7	9.7.4.8	9.7.4.9	9.7.5.1	9.7.5.2	9.7.5.3	9.7.5.4	9.7.5.5	9.7.5.6
9.7.5.7	9.7.5.8	9.7.5.9	9.7.6.1	9.7.6.2	9.7.6.3	9.7.6.4	9.7.6.5	9.7.6.6	9.7.6.7
9.7.6.8	9.7.6.9	9.7.7.1	9.7.7.2	9.7.7.3	9.7.7.4	9.7.7.5	9.7.7.6	9.7.7.7	9.7.7.8
9.7.7.9	9.7.8.1	9.7.8.2	9.7.8.3	9.7.8.4	9.7.8.5	9.7.8.6	9.7.8.7	9.7.8.8	9.7.8.9
9.7.9.1	9.7.9.2	9.7.9.3	9.7.9.4	9.7.9.5	9.7.9.6	9.7.9.7	9.7.9.8	9.7.9.9	9.8.1.1
9.8.1.2	9.8.1.3	9.8.1.4	9.8.1.5	9.8.1.6	9.8.1.7	9.8.1.8	9.8.1.9	9.8.2.1	9.8.2.2
9.8.2.3	9.8.2.4	9.8.2.5	9.8.2.6	9.8.2.7	9.8.2.8	9.8.2.9	9.8.3.1	9.8.3.2	9.8.3.3
9.8.3.4	9.8.3.5	9.8.3.6	9.8.3.7	9.8.3.8	9.8.3.9	9.8.4.1	9.8.4.2	9.8.4.3	9.8.4.4
9.8.4.5	9.8.4.6	9.8.4.7	9.8.4.8	9.8.4.9	9.8.5.1	9.8.5.2	9.8.5.3	9.8.5.4	9.8.5.5
9.8.5.6	9.8.5.7	9.8.5.8	9.8.5.9	9.8.6.1	9.8.6.2	9.8.6.3	9.8.6.4	9.8.6.5	9.8.6.6
9.8.6.7	9.8.6.8	9.8.6.9	9.8.7.1	9.8.7.2	9.8.7.3	9.8.7.4	9.8.7.5	9.8.7.6	9.8.7.7
9.8.7.8	9.8.7.9	9.8.8.1	9.8.8.2	9.8.8.3	9.8.8.4	9.8.8.5	9.8.8.6	9.8.8.7	9.8.8.8
9.8.8.9	9.8.9.1	9.8.9.2	9.8.9.3	9.8.9.4	9.8.9.5	9.8.9.6	9.8.9.7	9.8.9.8	9.8.9.9
9.9.1.1	9.9.1.2	9.9.1.3	9.9.1.4	9.9.1.5	9.9.1.6	9.9.1.7	9.9.1.8	9.9.1.9	9.9.2.1
9.9.2.2	9.9.2.3	9.9.2.4	9.9.2.5	9.9.2.6	9.9.2.7	9.9.2.8	9.9.2.9	9.9.3.1	9.9.3.2
9.9.3.3	9.9.3.4	9.9.3.5	9.9.3.6	9.9.3.7	9.9.3.8	9.9.3.9	9.9.4.1	9.9.4.2	9.9.4.3
9.9.4.4	9.9.4.5	9.9.4.6	9.9.4.7	9.9.4.8	9.9.4.9	9.9.5.1	9.9.5.2	9.9.5.3	9.9.5.4
9.9.5.5	9.9.5.6	9.9.5.7	9.9.5.8	9.9.5.9	9.9.6.1	9.9.6.2	9.9.6.3	9.9.6.4	9.9.6.5
9.9.6.6	9.9.6.7	9.9.6.8	9.9.6.9	9.9.7.1	9.9.7.2	9.9.7.3	9.9.7.4	9.9.7.5	9.9.7.6
9.9.7.7	9.9.7.8	9.9.7.9	9.9.8.1	9.9.8.2	9.9.8.3	9.9.8.4	9.9.8.5	9.9.8.6	9.9.8.7
9.9.8.8	9.9.8.9	9.9.9.1	9.9.9.2	9.9.9.3	9.9.9.4	9.9.9.5	9.9.9.6	9.9.9.7	9.9.9.8
9.9.9.9									

[0351] In another aspect the following compounds are included in the invention but the compounds are not limited to these illustrative compounds. The compounds are shown without depiction of stereochemistry since the compounds are biologically active as the diastereomeric mixture or as a single stereoisomer. Compounds included are designated by numbers assigned to the variables of formulas XI - XVI using the following convention: V1.V2.V3.V4.V5.V6. Each individual compound from 1.1.1.1.1.1 to 9.9.9.9.9.9 (*e.g.*, 2.3.4.5.6.7. or 8.7.3.5.2.1) is included in the present invention as an individual species and may be specifically set forth as such for inclusion or may be specifically excluded from the present invention. As the understanding is to what is included is clear from the description thus, a Table is not included so as to not unduly lengthen the specification.



Formula XI



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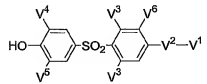
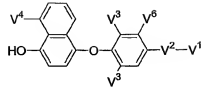
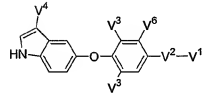


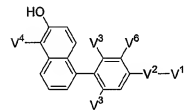
Formula XIII



Formula XIV



Formula XV



Formula XVI

[0352] Variable V^1:

1) -P(O)(OH)(CH_3)
2) -P(O)(OH)(CH_2CH_3)
3) -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3)
4) -P(O)[-$OCH_2OC(O)OCH(CH_3)_2$](CH_3)
5) -P(O)[-$OCH(CH_3)OC(O)C(CH_3)_3$](CH_3)
6) -P(O)[-$OCH(CH_3)OC(O)OCH(CH_3)_2$]($CH_3$)
7) -P(O)[-$N(H)CH(CH_3)C(O)OCH_2CH_3$]($CH_3$)
8) -P(O)[-$N(H)C(CH_3)_2C(O)OCH_2CH_3$]($CH_3$)
9) -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_2CH_3)

[0353] Variable V^2:

1) -CH_2-
2) -OCH_2-
3) -CH_2-CH_2-
4) -$NHCH_2$-
5) -NH(CO)-
6) -CH_2-$CH(NH_2)$- (*R*-configuration)
7) -CH_2-$CH(NH_2)$- (*S*-configuration)
8) -CH=CH- (*trans*)
9) - null

[0354] Variable V^3:

1) -OCH_3
2) iodo
3) bromo
4) chloro
5) fluoro
6) methyl
7) trifluoromethyl
8) cyano
9) -OCF_3

[0355] Variable V^4:

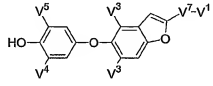
1) iodo
2) $CH(CH_3)_2$
3) -(3-trifluoromethylphenoxy)
4) -(3-ethylphenyl)
5) -C(O)NH-CH_2-CH_2-phenyl
6) -CH(OH)(4-fluorophenyl)
7) -SO_2(4-fluorophenyl)
8) -(4-fluorobenzyl)
9) -1-ethyl-propyl

[0356] Variable V^5 and V^6

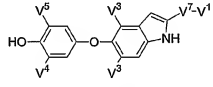
1) hydrogen
2) iodo
3) bromo
4) chloro
5) fluoro
6) methyl
7) trifluoromethyl
8) cyano
9) $-OCH_3$

[0357] In another aspect the following compounds are included in the invention but the compounds are not limited to these illustrative compounds. The compounds are shown without depiction of stereochemistry since the compounds are biologically active as the diastereomeric mixture or as a single stereoisomer. Compounds included are designated by numbers assigned to the variables of formulas XVII and XVIII using the following eonvention: $V^1.V^2.V^3.V^4.V^5.V^6.V^7$ Each individual compound from 1.1.1.1.1.1.1 to 9.9.9.9.9.9.2 (*e.g.*, 2.3.4.5.6.7.1 or 8.7.3.5.2.1.1) is included in the present invention as an individual species and may be specifically set forth as such for inclusion or may be specifically excluded from the present invention. As the

understanding is to what is included is clear from the description thus, a Table is not included so as to not unduly lengthen the specification.



Formula XVII



Formula XVIII

[0358] Variable V^7:

1) $-CH_2-$

2) - null

[0359] The present invention provides for compounds of Formula I including but not limited to wherein:

[0360] Phosphinic Acids

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)OH(CH_3)$;

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is $-P(O)OH(CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)OH(CH_3)$;

G is -O-, T is -N(H)C(O)-, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is CH(OH) (4-fluorophenyl), R^4 is -H, R^5 is -OH, X is $-P(O)OH(CH_3)$;

G is $-CH_2-$, T is $-OCH_2-$, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)OH(CH_3)$;

G is -O-, T is -CH_2-, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is –P(O)OH(CH_3);

G is -O-, T is -OCH_2-, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is –P(O)OH(CH_3);

[0361] POM Esters

G is -O-, T is -$CH_2CH(NH_2)$-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -$CH_2CH(NH_2)$-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -CH_2-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -N(H)C(O)-, R^1 is -CH_3, R^2 is -CH_3, R^3 is CH(OH)(4-fluorophenyl), R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

G is -CH_2-, T is -OCH_2-, R^1 is -CH_3, R^2 is -CH_3, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -CH_2-, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -OCH_2-, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH_2OC(O)C(CH_3)_3$](CH_3);

[0362] POM Esters #2

G is -O-, T is -$CH_2CH(NH_2)$-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH(CH_3)OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -$CH_2CH(NH_2)$-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is -P(O)[-$OCH(CH_3)OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -CH_2-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH(CH_3)OC(O)C(CH_3)_3$](CH_3);

G is -O-, T is -N(H)C(O)-, R^1 is -CH_3, R^2 is -CH_3, R^3 is CH(OH)(4-fluorophenyl), R^4 is -H, R^5 is -OH, X is -P(O)[-$OCH(CH_3)OC(O)C(CH_3)_3$](CH_3);

G is $-CH_2-$, T is $-OCH_2-$, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)C(CH_3)_3](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)C(CH_3)_3](CH_3)$;

G is -O-, T is $-OCH_2-$, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)C(CH_3)_3](CH_3)$;

[0363] Carbonates

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-N(H)C(O)-$, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is CH(OH)(4-fluorophenyl), R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

G is $-CH_2-$, T is $-OCH_2-$, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-OCH_2-$, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH_2OC(O)OCH(CH_3)_2](CH_3)$;

[0364] Carbonates #2

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is -N(H)C(O)-, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is CH(OH)(4-fluorophenyl), R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

G is $-CH_2-$, T is $-OCH_2-$, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

G is -O-, T is $-OCH_2-$, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[-OCH(CH_3)OC(O)OCH(CH_3)_2](CH_3)$;

[0365] Amidates

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is -N(H)C(O)-, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is CH(OH) (4-fluorophenyl), R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

G is $-CH_2-$, T is $-OCH_2-$, R^1 is $-CH_3$, R^2 is $-CH_3$, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is $-CH_2-$, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is $-OCH_2-$, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)CH(CH_3)C(O)OCH_2CH_3](CH_3)$;

[0366] Amidates #2

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is $-P(O)[N(H)C(CH_3)_2C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is $-CH_2CH(NH_2)-$, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -I, R^5 is -OH, X is $-P(O)[N(H)C(CH_3)_2C(O)OCH_2CH_3](CH_3)$;

G is -O-, T is -CH_2-, R^1 is -I, R^2 is -I, R^3 is -I, R^4 is -H, R^5 is -OH, X is -P(O)[N(H)C$(CH_3)_2$C(O)OCH_2CH_3](CH_3);

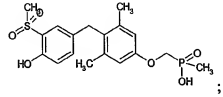
G is -O-, T is -N(H)C(O)-, R^1 is -CH_3, R^2 is -CH_3, R^3 is CH(OH) (4-fluorophenyl), R^4 is -H, R^5 is -OH, X is -P(O)[N(H)C$(CH_3)_2$C(O)OCH_2CH_3](CH_3);

G is -CH_2-, T is -OCH_2-, R^1 is -CH_3, R^2 is -CH_3, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is -P(O)[N(H)C$(CH_3)_2$C(O)OCH_2CH_3](CH_3);

G is -O-, T is -CH_2-, R^1 is -Cl, R^2 is -Cl, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is -P(O)[N(H)C$(CH_3)_2$C(O)OCH_2CH_3](CH_3);

G is -O-, T is -OCH_2-, R^1 is -I, R^2 is -I, R^3 is i-propyl, R^4 is -H, R^5 is -OH, X is -P(O)[N(H)C$(CH_3)_2$C(O)OCH_2CH_3](CH_3).

[0367] In one aspect, the invention relates to compounds selected from the group consisting of: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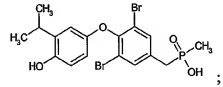
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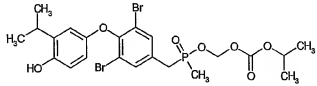
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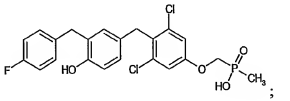
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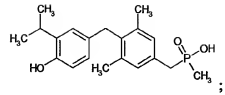
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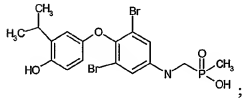
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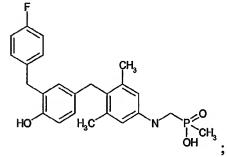
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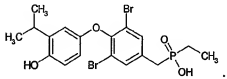
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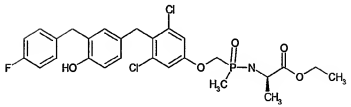
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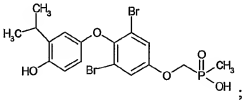
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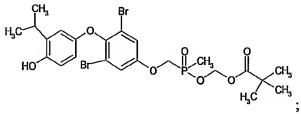
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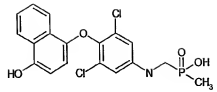
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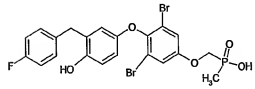
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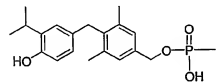
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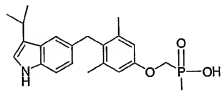
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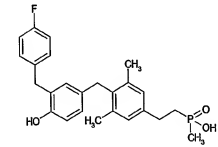
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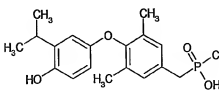
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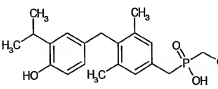
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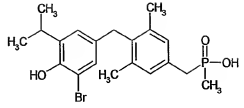
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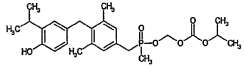
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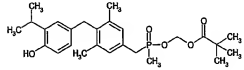
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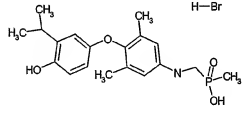
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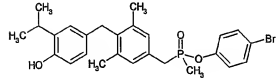
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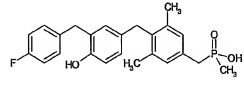
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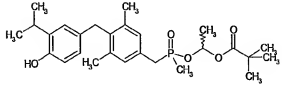
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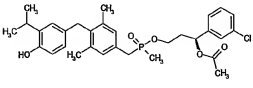
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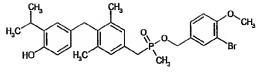
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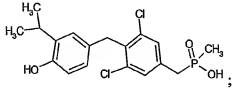
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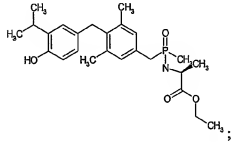
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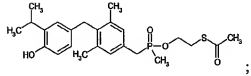
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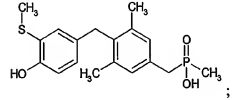
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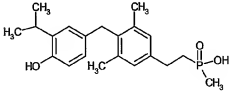
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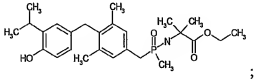
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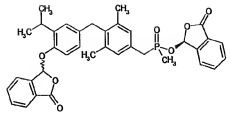
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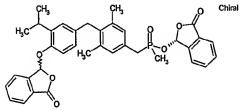
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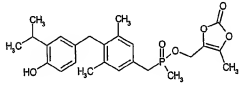
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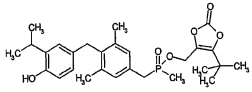
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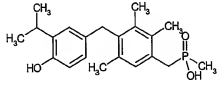
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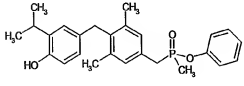
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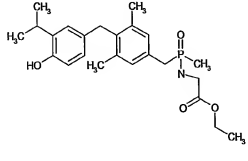
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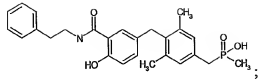
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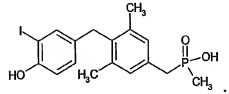
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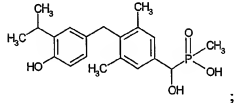
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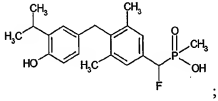
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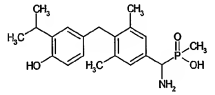


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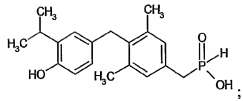
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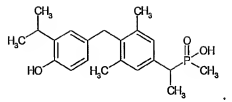
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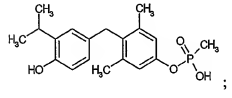
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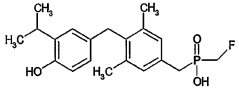
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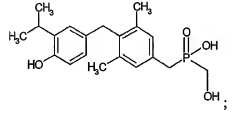
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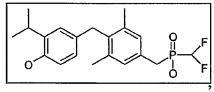
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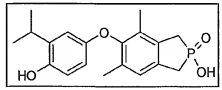
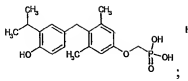


and pharmaceutically acceptable salts and prodrugs thereof. In one embodiment, the prodrugs of the above listed compounds are POM ester, carbonate, or amidate prodrugs.

[0368] In one aspect, the invention relates to phosphinic acid derivatives of phosphonic acid compounds selected from the group consisting of: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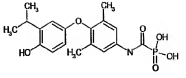
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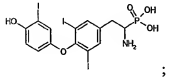
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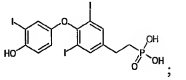
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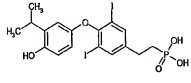
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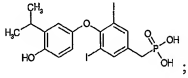
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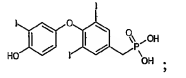
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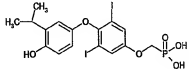
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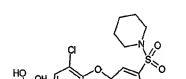
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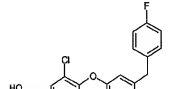
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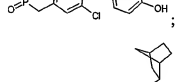
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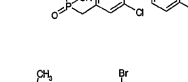
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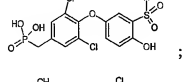
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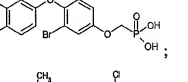
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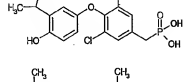
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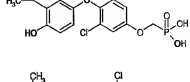
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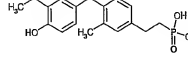
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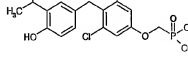
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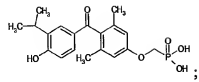
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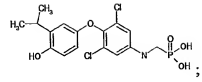
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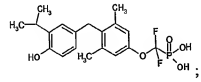
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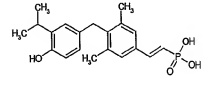
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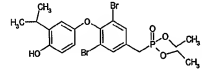
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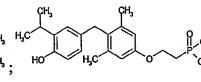
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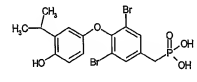
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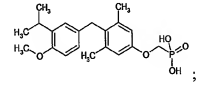
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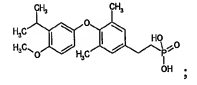
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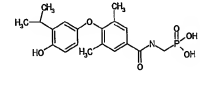
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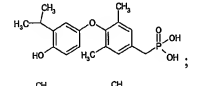
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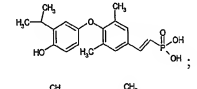
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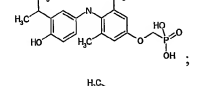
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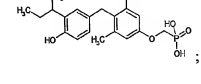
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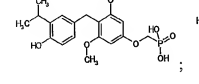
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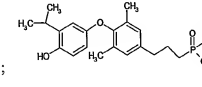
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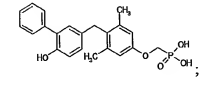
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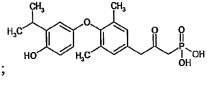
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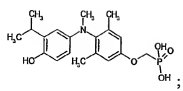
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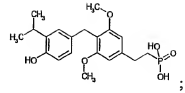
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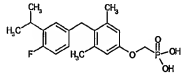
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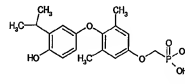
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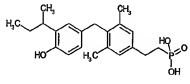
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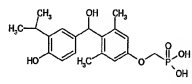
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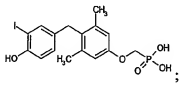
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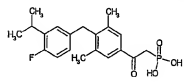
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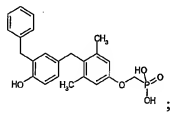
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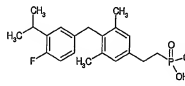
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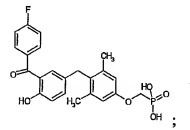
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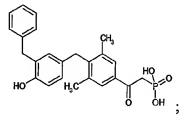
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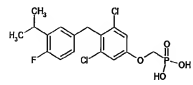
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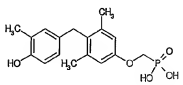
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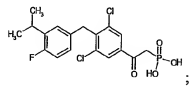
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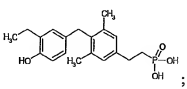
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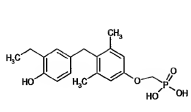
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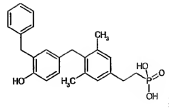
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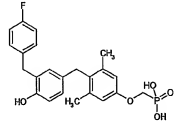
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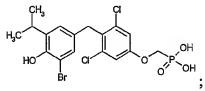
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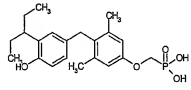
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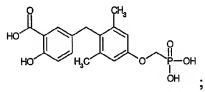
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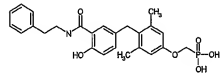
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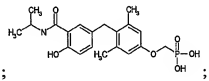
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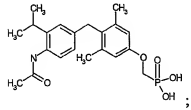
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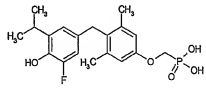
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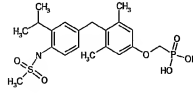
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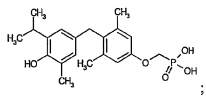
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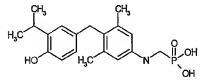
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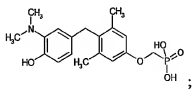
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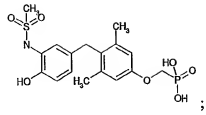
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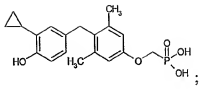
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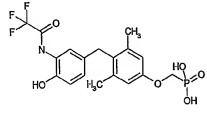
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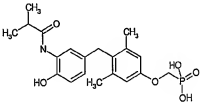
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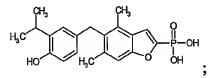
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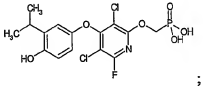
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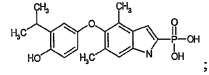
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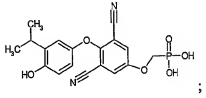
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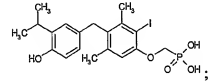
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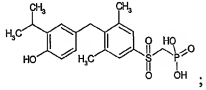
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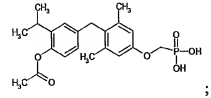
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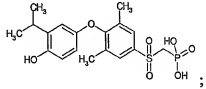
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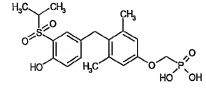
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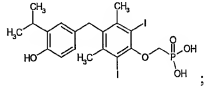
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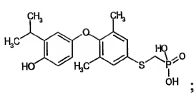
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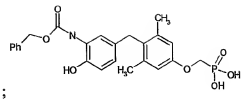
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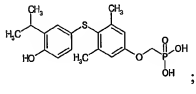
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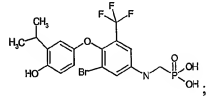
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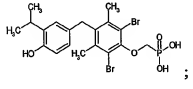
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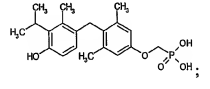
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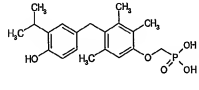
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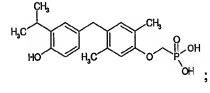
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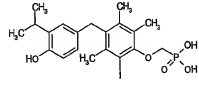
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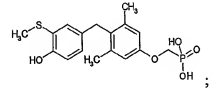
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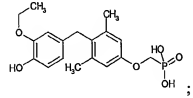
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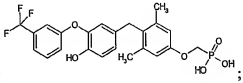
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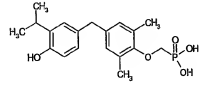
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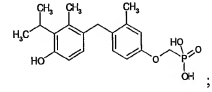
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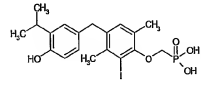
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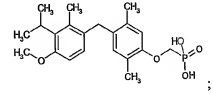
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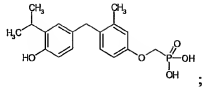
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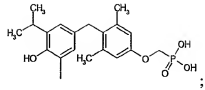
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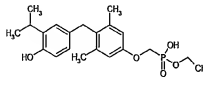
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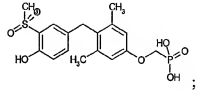
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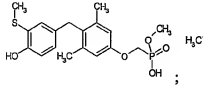
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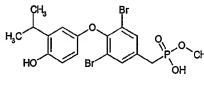
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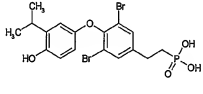
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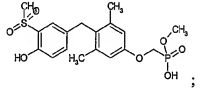
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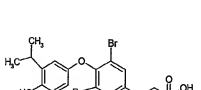
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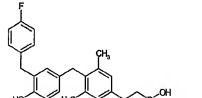
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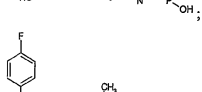
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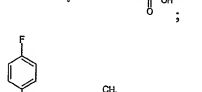
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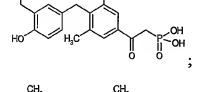
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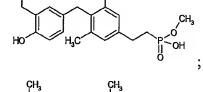
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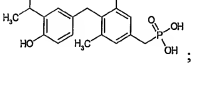
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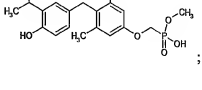
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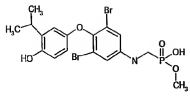
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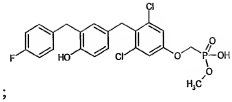
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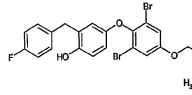
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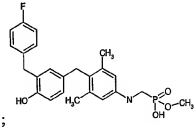
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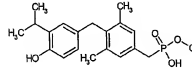
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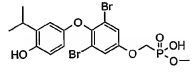
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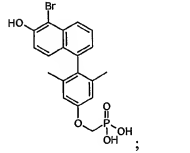
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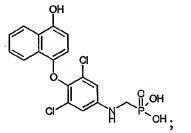
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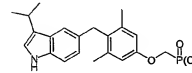
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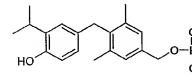
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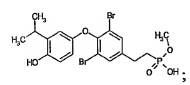
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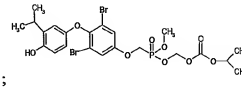
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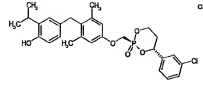
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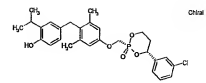
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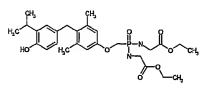
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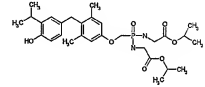
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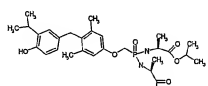
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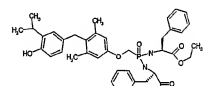
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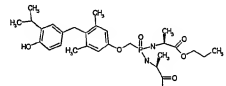
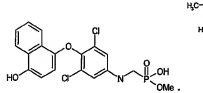
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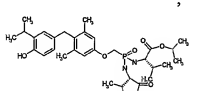
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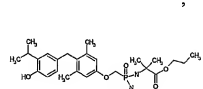
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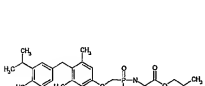
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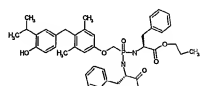
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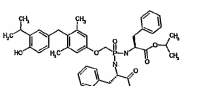
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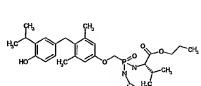
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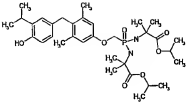
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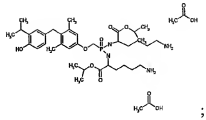
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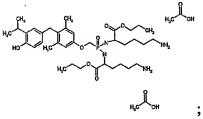
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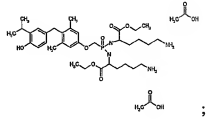
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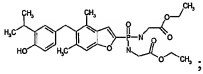
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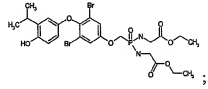
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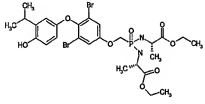
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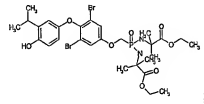
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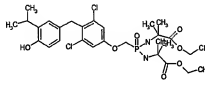
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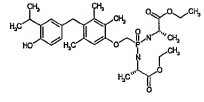
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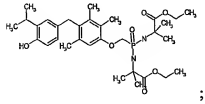
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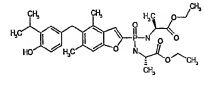
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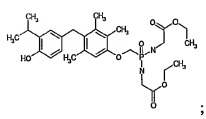
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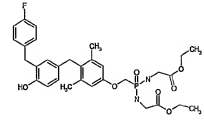
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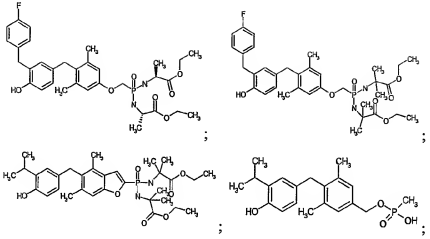


and prodrugs of the compounds, and pharmaceutically acceptable salts thereof. In one embodiment, the prodrugs are bisPOM, carbonate, or bisamidate prodrugs of the compounds.

[0369] In another aspect, the invention relates to phosphinic acid derivatives of each of the compounds exemplified in Examples 1-116. The invention further relates to phosphinic acid prodrugs of each of the exemplified compounds utilizing the prodrug moieties discussed above.

[0370] Moreover, the compounds of the present invention can be administered in combination with other pharmaceutical agents that are used to lower serum cholesterol such as a cholesterol biosynthesis inhibitor or a cholesterol absorption inhibitor, especially a HMG-CoA reductase inhibitor, or a HMG-CoA synthase inhibitor, or a HMG-CoA reductase or synthase gene expression inhibitor, a cholesteryl ester transfer protein (CETP) inhibitor (e.g., torcetrapib), a bile acid sequesterant (e.g., cholestyramine (Questran®), colesevelam and colestipol (Colestid®)), or a bile acid reabsorption inhibitor (see, for example, U.S. Pat. No. 6,245,744, U.S. Pat. No. 6,221,897, U.S. Pat. No. 6,277,831, EP 0683 773, EP 0683 774), a cholesterol absorption inhibitor as described (e.g., ezetimibe, tiqueside, pamaqueside or see, e.g., in WO 0250027), a PPARalpha agonist, a mixed PPAR alpha/gamma agonist such as, for example, AZ 242 (Tesaglitazar, (S)-3-(4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl)-2-ethoxypropionic acid), BMS 298585 (N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-

oxazolyl)ethoxy]phenyl]methyl]glycine) or as described in WO 99/62872, WO 99/62871, WO 01/40171, WO 01/40169, WO96/38428, WO 01/81327, WO 01/21602, WO 03/020269, WO 00/64888 or WO 00/64876, a MTP inhibitor such as, for example, implitapide, a fibrate, an ACAT inhibitor (e.g., avasimibe), an angiotensin II receptor antagonist, a squalene synthetase inhibitor, a squalene epoxidase inhibitor, a squalene cyclase inhibitor, combined squalene epoxidase/squalene cyclase inhibitor, a lipoprotein lipase inhibitor, an ATP citrate lyase inhibitor, lipoprotein(a) antagonist, an antioxidant or niacin (e.g., slow release niacin). The compounds of the present invention may also be administered in combination with a naturally occurring compound that act to lower plasma cholesterol levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract and niacin.

[0371] In one aspect, the HMG-CoA reductase inhibitor is from a class of therapeutics commonly called statins. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR; see U.S. Pat. Nos. 4,231,938; 4,294,926; 4,319,039), simvastatin (ZOCOR; see U.S. Pat. Nos. 4,444,784; 4,450,171, 4,820,850; 4,916,239), pravastatin (PRAVACHOL; see U.S. Pat. Nos. 4,346,227; 4,537,859; 4,410,629; 5,030,447 and 5,180,589), lactones of pravastatin (see U.S. Pat. No. 4,448,979), fluvastatin (LESCOL; see U.S. Pat. Nos. 5,354,772; 4,911,165; 4,739,073; 4,929,437; 5,189,164; 5,118,853; 5,290,946; 5,356,896), lactones of fluvastatin, atorvastatin (LIPITOR; see U.S. Pat. Nos. 5,273,995; 4,681,893; 5,489,691; 5,342,952), lactones of atorvastatin, cerivastatin (also known as rivastatin and BAYCHOL; see U.S. Pat. No. 5,177,080, and European Application No. EP-491226A), lactones of cerivastatin, rosuvastatin (CRESTOR; see U.S. Pat. Nos. 5,260,440 and RE37314, and European Patent No. EP521471), lactones of rosuvastatin, itavastatin, nisvastatin, visastatin, atavastatin, bervastatin, compactin, dihydrocompactin, dalvastatin, fluindostatin, pitivastatin, mevastatin (see U.S. Pat. No. 3,983,140), and velostatin (also referred to as synvinolin). Other examples of HMG-CoA reductase inhibitors are described in U.S. Pat. Nos.

5,217,992; 5,196,440; 5,189,180; 5,166,364; 5,157,134; 5,110,940; 5,106,992; 5,099,035; 5,081,136; 5,049,696; 5,049,577; 5,025,017; 5,011,947; 5,010,105; 4,970,221; 4,940,800; 4,866,058; 4,686,237; 4,647,576; European Application Nos. 0142146A2 and 0221025A1; and PCT Application Nos. WO 86/03488 and WO 86/07054. Also included are pharmaceutically acceptable forms of the above. All of the above refcrences are incorporated herein by reference.

[0372] Non-limiting examples of suitable bile acid sequestrants include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN or QUESTRAN LIGHT cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl)alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof. Other useful bile acid sequestrants are disclosed in PCT Patent Applications Nos. WO 97/11345 and WO 98/57652, and U.S. Pat. Nos. 3,692,895 and 5,703,188 which are incorporated herein by reference. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

[0373] In the above description, a fibrate base compound is a medicament for inhibiting synthesis and secretion of triglycerides in the liver and activating lipoprotein lipase, thereby lowering the triglyceride level in the blood. Examples include bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, ethofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate and theofibrate. Such an ACAT inhibitor includes, for example: a compound having the general formula (I) disclosed in WO 92/09561 [preferably FR-129169, of which the chemical name is N-(1,2-diphenylethyl)-2-(2-octyloxyphenyl)acetamide]; a compound

having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kohyo) Hei 8-510256 (WO 94/26702, U.S. Pat. No. 5,491,172) {preferably CI-1011, of which the chemical name is 2,6-diisopropylphenyl-N-[(2,4,6-triisopropylphenyl)acetyl]sulfamate, and in the present invention CI-1011 including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof; a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in EP 421441 (U.S. Pat. No. 5,120,738) {preferably F-1394, of which the chemical name is (1S,2S)-2-[3-(2,2-dimethylpropyl)-3-nonylureido]cyclohexan-1-yl 3-[(4R)-N-(2,2,5,5-tetramethyl-1,- 3-dioxane-4-carbonyl)amino]propionate, and in the present invention F-1394 including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a compound including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kohyo) 2000-500771 (WO 97/19918, U.S. Pat. No. 5,990,173) [preferably F-12511, of which the chemical name is (S)-2',3',5'-trimethyl-4'-hydroxy-α-dodecylthio-.alpha.-phenylacetanilide, and in the present invention F-12511 including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof]; a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Hei 10-195037 (EP 790240, U.S. Pat. No. 5,849,732) [preferably T-2591, of which the chemical name is 1-(3-t-butyl-2-hydroxy-5-methoxyphenyl)-3-(2-cyclohexylethyl)-3-(4-dimethylaminophenyl)urea, and in the present invention T-2591 including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof]; a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in WO 96/26948 {preferably FCE-28654, of which the chemical name is 1-(2,6-diisopropylphenyl)-3-[(4R,5R)-4,5-dimethyl-2-(4-phosphonophenyl)-1,3-dioxolan-2-ylmethyl]urea, including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a compound having the general formula (I)

or a pharmacologically acceptable salt thereof disclosed in the specification of WO 98/54153 (EP 987254) {preferably K-10085, of which the chemical name is N-[2,4-bis(methylthio)-6-methyl-3-pyridyl]-2-[4-[2-(oxazolo[4,5-b]pyridine-2-ylthio)ethyl]piperazin-1-yl]acetamide, including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a compound having the general formula (I) disclosed in WO 92/09572 (EP 559898, U.S. Pat. No. 5,475,130) [preferably HL-004, of which the chemical name is N-(2,6-diisopropylphenyl)-2-tetradecylthioacetamide]; a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Hei 7-82232 (EP 718281) {preferably NTE-122, of which the chemical name is trans-1,4-bis[1-cyclohexyl-3-(4-dimethylaminophenyl)ureidomethyl]cyclohexane, and in the present invention NTE-122 includes pharmacologically acceptable salts of NTE-122}; a compound including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kohyo) Hei 10-510512 (WO 96/10559) {preferably FR-186054, of which the chemical name is 1-benzyl-1-[3-(pyrazol-3-yl)benzyl]-3-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea, and in the present invention FR-186054 including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in WO 96/09287 (EP 0782986, U.S. Pat. No. 5,990,150) [preferably N-(1-pentyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide, and in the present invention including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof]; and a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in WO 97/12860 (EP 0866059, U.S. Pat. No. 6,063,806) [preferably N-(1-octyl-5-carboxymethyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide, including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof]. The ACAT inhibitor preferably is a compound selected from the group consisting of FR-129169, CI-1011, F-1394,

F-12511, T-2591, FCE-28654, K-10085, HL-004, NTE-122, FR-186054, N-(1-octyl-5-carboxymethyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide (hereinafter referred as compound A), and N-(1-pentyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide (hereinafter referred as compound B), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof. The ACAT inhibitor more preferably is a compound selected from the group consisting of CI-1011, F-12511, N-(1-octyl-5-carboxymethyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide (compound A), and N-(1-pentyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide (compound B), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof; most preferred is N-(1-octyl-5-carboxymethyl-4,6-dimethylindolin-7-yl)-2,2-dimethylpropaneamide (compound A).

[0374] An angiotensin II receptor antagonist includes, for example, a biphenyl tetrazole compound or biphenylcarboxylic acid derivative such as: a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Sho 63-23868 (U.S. Pat. No. 5,138,069) {preferably losartan, of which the chemical name is 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-imidazol-5-methanol, and in the present invention losartan including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof }; a compound having the general formula (I) including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kohyo) Hei 4-506222 (WO 91/14679) {preferably irbesartan, of which the chemical name is 2-N-butyl-4-spirocyclopentane-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazoline-5-one, and in the present invention irbesartan including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a compound having the general formula (I), an ester thereof, including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Hei 4-235149 (EP 433983) {preferably valsartan, of which the chemical name is (S)-N-valeryl-

N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]valine, and in the present invention valsartan including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a carboxylic acid derivative having the general formula (I), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Hei 4-364171 (U.S. Pat. No. 5,196,444) {preferably candesartan, of which the chemical name is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-benzimidazole-7-carboxylate, and in the present invention candesartan including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof (TCV-116 or the like), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof}; a carboxylic acid derivative having the general formula (I), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Hei 5-78328 (U.S. Pat. No. 5,616,599) {preferably olmesartan, of which the chemical name is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate, and in the present invention olmesartan includes carboxylic acid derivatives thereof, pharmacologically acceptable esters of the carboxylic acid derivatives (CS-866 or the like), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof }; and a compound having the general formula (I), including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof disclosed in the Japanese Patent Publication (Kokai) Hei 4-346978 (U.S. Pat. No. 5,591,762, EP 502,314) {preferably telmisartan, of which the chemical name is 4'-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]- methyl]biphenyl-2-carboxylate, including a pharmacologically acceptable salt/co-crystal, ester or prodrug thereof }. The angiotensin II receptor antagonist preferably is losartan, irbesartan, valsartan, candesartan, olmesartan, or telmisartan; more preferred is losartan or olmesartan; and most preferred is olmesartan.

[0375] In addition to being useful in treating or preventing certain diseases and disorders, combination therapy with compounds of this invention maybe useful in reducing the dosage of the second drug or agent (*e.g.*, atorvastatin).

[0376] In addition, the compounds of the present invention can be used in combination with an apolipoprotein B secretion inhibitor and/or microsomal triglyceride transfer protein (MTP) inhibitor. Some apolipoprotein B secretion inhibitors and/or MTP inhibitors are disclosed in U.S. 5,919,795.

[0377] Any HMG-CoA reductase inhibitor may be employed as an additional compound in the combination therapy aspect of the present invention. The term HMG-CoA reductase inhibitor refers to a compound that inhibits the biotransformation of hydroxymethylglutaryl-coenzyme A to mevalonic acid as catalyzed by the enzyme HMG-CoA reductase. Such inhibition may be determined readily by one of skill in the art according to standard assays (*e.g.*, *Methods of Enzymology*, 71: 455—509 (1981); and the references cited therein). A variety of these compounds are described and referenced below. U.S. 4,231,938 discloses certain compounds isolated after cultivation of a microorganism belonging to the genus Aspergillus, such as lovastatin. Also U.S. 4,444,784 discloses synthetic derivatives of the aforementioned compounds, such as simvastatin. Additionally, U.S. 4,739,073 discloses certain substituted indoles, such as fluvastatin. Further, U.S. 4,346,227 discloses ML-236B derivatives, such as pravastatin. In addition, EP 491,226 teaches certain pyridyldihydroxyheptenoic acids, such as rivastatin. Also, U.S. 4,647,576 discloses certain 6-[2-(substituted-pyrrol-1-yl)-alkyl]-pyran-2-ones such as atorvastatin. Other HMG-CoA reductase inhibitors will be known to those skilled in the art. Examples of currently or previously marketed products containing HMG-CoA reductase inhibitors include cerivastatin Na, rosuvastatin Ca, fluvastatin, atorvastatin, lovastatin, pravastatin Na and simvastatin.

[0378] Any HMG-CoA synthase inhibitor may be used as an additional compound in the combination therapy aspect of this invention. The term HMG-CoA synthase inhibitor refers to a compound that inhibits the biosynthesis of hydroxymethylglutaryl-coenzyme A from acetyl-coenzyme A

and acetoacetyl-coenzyme A, catalyzed by the enzyme HMG-CoA synthase. Such inhibition may be determined readily by one of skill in the art according to standard assays (*e.g., Methods of Enzymology* 35: 155-160 (1975); and *Methods of Enzymology,* 110: 19-26 *(1985);* and the references cited therein). A variety of these compounds are described and referenced below. U.S. 5,120,729 discloses certain beta-lactam derivatives. U.S. 5,064,856 discloses certain spiro-lactone derivatives prepared by culturing the microorganism MF5253. U.S. 4,847,271 discloses certain oxetane compounds such as 11-(3-hydroxymethyl-4-oxo-2-oxetayl)-3,5,7-trimethyl-2,4-undecadienoic acid derivatives. Other HMG-CoA synthase inhibitors useful in the methods, compositions and kits of the present invention will be known to those skilled in the art.

[0379] Any compound that decreases HMG-CoA reductase gene expression may be used as an additional compound in the combination therapy aspect of this invention. These agents may be HMG-CoA reductase transcription inhibitors that block the transcription of DNA or translation inhibitors that prevent translation of mRNA coding for HMG-CoA reductase into protein. Such inhibitors may either affect transcription or translation directly, or may be biotransformed into compounds that have the aforementioned attributes by one or more enzymes in the cholesterol biosynthetic cascade or may lead to the accumulation of an isoprene metabolite that has the aforementioned activities. Such regulation is readily determined by those skilled in the art according to standard assays *(Methods of Enzymology,* 110: 9-19 (1985)). Several such compounds are described and referenced below; however, other inhibitors of HMG-CoA reductase gene expression will be known to those skilled in the art, for example, U.S. 5,041,432 discloses certain 15-substituted lanosterol derivatives that are inhibitors of HMG-CoA reductase gene expression. Other oxygenated sterols that suppress the biosynthesis of HMG-CoA reductase are discussed by E. I. Mercer *(Prog. Lip. Res.,* 32:357-416 (1993)).

[0380] Any compound having activity as a CETP inhibitor can serve as the second compound in the combination therapy aspect of the instant invention.

The term CETP inhibitor refers to compounds that inhibit the cholesteryl ester transfer protein (CETP) mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. A variety of these compounds are described and referenced below; however, other CETP inhibitors will be known to those skilled in the art. U.S. 5,512,548 discloses certain polypeptide derivatives having activity as CETP inhibitors, while certain CETP-inhibitory rosenonolactone derivatives and phosphate-containing analogs of cholesteryl ester are disclosed in *J. Antibiot.*, 49(8): 815-816 (1996), and *Bioorg. Med. Chem. Lett.*, 6:1951-1954 (1996), respectively.

[0381] Any ACAT inhibitor can serve as an additional compound in the combination therapy aspect of this invention. The term ACAT inhibitor refers to a compound that inhibits the intracellular esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase. Such inhibition may be determined readily by one of skill in the art according to standard assays, such as the method of Heider *et al.* described in *Journal of Lipid Research*, 24:1127 (1983). A variety of these compounds are described and referenced below; however, other ACAT inhibitors will be known to those skilled in the art. U.S. 5,510,379 discloses certain carboxysulfonates, while WO 96/26948 and WO 96/10559 both disclose urea derivatives having ACAT inhibitory activity.

[0382] Any compound having activity as a squalene synthetase inhibitor can serve as an additional compound in the combination therapy aspect of the instant invention. The term squalene synthetase inhibitor refers to compounds that inhibit the condensation of two molecules of famesylpyrophosphate to form squalene, a reaction that is catalyzed by the enzyme squalene synthetase. Such inhibition is readily determined by those skilled in the art according to standard methodology *(Methods of Enzymology* 15:393-454 (1969); and *Methods of Enzymology* 110: 359-373 (1985); and references cited therein). A summary of squalene synthetase inhibitors has been complied in *Curr. Op. Ther Patents*, 861-4, (1993). EP 0 567 026 Al discloses certain 4,1-benzoxazepine derivatives as squalene synthetase inhibitors and their use in the treatment of hypercholesterolemia and as fungicides. EP 0 645 378 Al

discloses certain seven- or eight-membered heterocycles as squalene synthetase inhibitors and their use in the treatment and prevention hypercholesterolemia and fungal infections. EP 0 645 377 Al discloses certain benzoxazepine derivatives as squalene synthetase inhibitors useful for the treatment of hypercholesterolemia or coronary sclerosis. EP 0 611 749 Al discloses certain substituted amic acid derivatives useful for the treatment of arteriosclerosis. EP 0 705 607 A2 discloses certain condensed seven- or eight-membered heterocyclic compounds useful as antihypertriglyceridemic agents. WO 96/09827 discloses certain combinations of cholesterol absorption inhibitors and cholesterol biosynthesis inhibitors including benzoxazepine derivatives and benzothiazepine derivatives. EP 0 701 725 Al discloses a process for preparing certain optically-active compounds, including benzoxazepine derivatives, having plasma cholesterol and triglyceride lowering activities.

[0383] Other compounds that are currently or previously marketed for hyperlipidemia, including hypercholesterolemia, and which are intended to help prevent or treat atherosclerosis, include bile acid sequestrants, such as colestipol HCl and cholestyramine; and fibric acid derivatives, such as clofibrate, fenofibrate, and gemfibrozil. These compounds can also be used in combination with a compound of the present invention.

[0384] It is also contemplated that the compounds of the present invention be administered with a lipase inhibitor and/or a glucosidase inhibitor, which are typically used in the treatment of conditions resulting from the presence of excess triglycerides, free fatty acids, cholesterol, cholesterol esters or glucose including, inter alia, obesity, hyperlipidemia, hyperlipoproteinemia, Syndrome X, and the like.

[0385] In a combination with a compound of the present invention, any lipase inhibitor or glucosidase inhibitor may be employed. In one aspect lipase inhibitors comprise gastric or pancreatic lipase inhibitors. In a further aspect glucosidase inhibitors comprise amylase inhibitors. Examples of glucosidase inhibitors are those inhibitors selected from the group consisting of acarbose, adiposine, voglibose, miglitol, emiglitate, camiglibose, tendamistate, trestatin,

pradimicin-Q and salbostatin. Examples of amylase inhibitors include tendamistat and the various cyclic peptides related thereto disclosed in U.S. Pat. No. 4,451,455, AI-3688 and the various cyclic polypeptides related thereto disclosed in U.S. Pat. No. 4,623,714, and trestatin, consisting of a mixture of trestatin A, trestatin B and trestatin C and the various trehalose-containing aminosugars related thereto disclosed in U.S. Pat. No. 4,273,765.

[0386] A lipase inhibitor is a compound that inhibits the metabolic cleavage of dietary triglycerides into free fatty acids and monoglycerides. Under normal physiological conditions, lipolysis occurs via a two-step process that involves acylation of an activated serine moiety of the lipase enzyme. This leads to the production of a fatty acid-lipase hemiacetal intermediate, which is then cleaved to release a diglyceride. Following further deacylation, the lipase-fatty acid intermediate is cleaved, resulting in free lipase, a monoglyceride and a fatty acid. The resultant free fatty acids and monoglycerides are incorporated into bile acid phospholipid micelles, which are subsequently absorbed at the level of the brush border of the small intestine. The micelles eventually enter the peripheral circulation as chylomicrons. Accordingly, compounds, including lipase inhibitors that selectively limit or inhibit the absorption of ingested fat precursors are useful in the treatment of conditions including obesity, hyperlipidemia, hyperlipoproteinemia, Syndrome X, and the like.

[0387] Pancreatic lipase mediates the metabolic cleavage of fatty acids from triglycerides at the 1- and 3-carbon positions. The primary site of the metabolism of ingested fats is in the duodenum and proximal jejunum by pancreatic lipase, which is usually secreted in vast excess of the amounts necessary for the breakdown of fats in the upper small intestine. Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions.

[0388] Gastric lipase is an immunologically distinct lipase that is responsible for approximately 10 to 40% of the digestion of dietary fats. Gastric lipase is secreted in response to mechanical stimulation, ingestion of food, the presence

of a fatty meal or by sympathetic agents. Gastric lipolysis of ingested fats is of physiological importance in the provision of fatty acids needed to trigger pancreatic lipase activity in the intestine and is also of importance for fat absorption in a variety of physiological and pathological conditions associated with pancreatic insufficiency. See, for example, C. K. Abrams, *et al.*, *Gastroenterology* 92: 125 (1987).

[0389] A variety of lipase inhibitors are known to one of ordinary skill in the art. However, in the practice of the methods, pharmaceutical compositions, and kits of the instant invention, generally lipase inhibitors are those inhibitors that are selected from the group consisting of lipstatin, tetrahydrolipstatin (orlistat), FL-386, WAY-121898, Bay-N-3176, valilactone, esterastin, ebelactone A, ebelactone B and RHC 80267.

[0390] The pancreatic lipase inhibitors lipstatin, 2S, 3S, *SS*, 7Z,1OZ)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,1(t-hexadecanoic acid lactone, and tetrahydrolipostatin (orlistat), 2S, 3S, 55)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic acid lactone, and the variously substituted N-formylleucine derivatives and stereoisomers thereof, are disclosed in U.S. 4,598,089.

[0391] The pancreatic lipase inhibitor FL-386, 1-[4-(2-methylpropyl)cyclohexyl]-2-[(phenylsulfonyl)oxy]-ethanone, and the variously substituted sulfonate derivatives related thereto, are disclosed in U.S. 4,452,813.

[0392] The pancreatic lipase inhibitor WAY-121898, 4-phenoxyphenyl-4-methylpiperidin-1-yl-carboxylate, and the various carbamate esters and pharmaceutically acceptable salts related thereto, are disclosed in U.S. 5,512,565; 5,391,571 and 5,602,151.

[0393] The lipase inhibitor Bay-N-3176, N-3-trifiuoromethylphenyl-N'-3-chloro-4-trifiuorometbylphenylurea, and the various urea derivatives related thereto, are disclosed in U.S. 4,405,644.

[0394] The pancreatic lipase inhibitor valilactone, and a process for the preparation thereof by the microbial cultivation of Aetinomycetes strain

MG147—CF2, are disclosed in Kitahara, *et al., J. Antibiotics,* 40(11): 1647-50 (1987).

[0395] The lipase inhibitor esteracin, and certain processes for the preparation thereof by the microbial cultivation of Streptomyces strain ATCC 31336, are disclosed in U.S. 4,189,438 and 4,242,453.

[0396] The pancreatic lipase inhibitors ebelactone A and ebelactone B, and a process for the preparation thereof by the microbial cultivation of Actinomycetes strain MG7-G1, are disclosed in Umezawa, *et al., J. Antibiotics,* 33, 1594-1596 (1980). The use of ebelactones A and B in the suppression of monoglyceride formation is disclosed in Japanese Kokai 08-143457, published Jun. 4, 1996.

[0397] The lipase inhibitor RHC 80267, cyclo-O,O'-[(1,6-hexanediyl)-bis-(iminocarbonyl)]dioxime, and the various bis(iminocarbonyl)dioximes related thereto may be prepared as described in Petersen *et al., Liebig's Annalen,* 562: 205-29 (1949).

[0398] The ability of RHC 80267 to inhibit the activity of myocardial lipoprotein lipase is disclosed in Carroll *et al., Lipids,* 27 305-7 (1992) and Chuang *et al., J. Mol. Cell Cardiol.,* 22: 1009-16 (1990).

[0399] In another aspect of the present invention, the compounds of Formula I can be used in combination with an additional anti-obesity agent. The additional anti-obesity agent in one aspect is selected from the group consisting of a β_3-adrenergic receptor agonist, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotoninergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a lipase inhibitor, a bombesin agonist, a neuropeptide-Y antagonist, a thyromimetic agent, dehydroepiandrosterone or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, and a ciliary neurotrophic factor.

[0400] In an additional aspect the anti-obesity agents comprise those compounds selected from the group consisting of sibutramine, fenfluramine, dexfenfluramine, bromocriptine, phentermine, ephedrine, leptin, phenylpropanolamine pseudoephedrine, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl} acetic acid, {4{2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}benzoic acid, {4-[2-(2{6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl} propionic acid, and {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenoxy} acetic acid.

[0401] In one aspect, the present invention concerns the prevention or treatment of diabetes, including impaired glucose tolerance, insulin resistance, insulin dependent diabetes mellitus (Type I) and non-insulin dependent diabetes mellitus (NIDDM or Type II). Also included in the prevention or treatment of diabetes are the diabetic complications, such as neuropathy, nephropathy, retinopathy or cataracts.

[0402] In one aspect the type of diabetes to be treated by the compounds of the present invention is non-insulin dependent diabetes mellitus, also known as Type II diabetes or NIDDM.

[0403] Diabetes can be treated by administering to a patient having diabetes (Type I or Type II), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a compound of the present invention. It is also contemplated that diabetes be treated by administering a compound of the present invention along with other agents that can be used to prevent or treat diabetes.

[0404] Representative agents that can be used to treat diabetes in combination with a compound of the present invention include insulin and insulin analogs (*e.g.*, LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36) — NH_2. Agents that enhance insulin secretion, *e.g.*, eblorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, nateglinide, meglitinide; biguanides: metformin, phenformin, buformin; A2-antagonists and imidazolines: midaglizole,

isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues linogliride, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, BRL49653; fatty acid oxidation inhibitors: clomoxir, etomoxir; a-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL25,637, camiglibose, MDL-73,945; ~3-agonists: BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: -386,398; lipid-lowering agents benfluorex; antiobesity agents: fenfiuramine; vanadate and vanadium complexes (*e.g.*, bis(cysteinamide N-octyl) oxovanadium) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994. Also contemplated to be used in combination with a compound of the present invention are pramlintide (symlin™), AC 2993 and nateglinide. Any agent or combination of agents can be administered as described above.

[0405] In addition, the compounds of the present invention can be used in combination with one or more aldose reductase inhibitors, DPPIV inhibitor, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, NHE-1 inhibitors and/or glucocorticoid receptor antagonists.

[0406] Any compound having activity as a fructose -1,6-bisphosphatase (FBPase) inhibitor can serve as the second compound in the combination therapy aspect of the instant invention (*e.g.*, 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis((*S*)-1-ethoxycarbonyl)ethyl)phosphonamido]furanyl}thiazoles).

FBPase is a key regulatory enzyme in gluconeogenesis, the metabolic pathway by which the liver synthesizes glucose from 3-carbon precursors. The term FBPase inhibitor refers to compounds that inhibit FBPase enzyme activity and thereby block the conversion of fructose -1,6-bisphosphate, the substrate of the enzyme, to fructose 6-phosphate. FBPase inhibition can be determined directly at the enzyme level by those skilled in the art according to standard methodology (*e.g.*, Gidh-Jain M, Zhang Y, van Poelje PD *et al.*, *J Biol Chem.* 1994, 269(44): 27732-8). Alternatively, FBPase inhibition can be assessed according to standard methodology by measuring the inhibition of glucose production by isolated hepatocytes or in a perfused liver, or by measuring

blood glucose lowering in normal or diabetic animals (*e.g.*, Vincent MF, Erion MD, Gruber HE, Van den Berghe, *Diabetologia*. 1996, 39(10):1148-55.; Vincent MF, Marangos PJ, Gruber HE, Van den Berghe G, *Diabetes* 1991 40(10):1259-66). In some cases, *in vivo* metabolic activation of a compound may be required to generate the FBPase inhibitor. This class of compounds may be inactive in the enzyme inhibition screen, may or may not be active in hepatocytes, but is active *in vivo* as evidenced by glucose lowering in the normal, fasted rat and/or in animal models of diabetes.

[0407] A variety of FBPase inhibitors are described and referenced below; however, other FBPase inhibitors will be known to those skilled in the art. Gruber *et al.* U.S. Patent No. 5,658,889 described the use of inhibitors of the AMP site of FBPase to treat diabetes; WO 98/39344 and US 6,284,748 describe purine inhibitors; WO 98/39343 and US 6,110,903 describe benzothiazole inhibitors to treat diabetes; WO 98/39342 and US 6,054,587 describe indole inhibitors to treat diabetes; and WO 00/14095 and US 6,489476 describe heteroaromatic phosphonate inhibitors to treat diabetes. Other FBPase inhibitors are described in Wright SW, Carlo AA, Carty MD *et al.*, *J Med Chem*. 2002 45(18):3865-77 and WO 99/47549.

[0408] The compounds of the present invention can also be used in combination with sulfonylureas such as amaryl, alyburide, glucotrol, chlorpropamide, diabinese, tolazamide, tolinase, acetohexamide, glipizide, tolbutamide, orinase, glimepiride, DiaBeta, micronase, glibenclamide, and gliclazide.

[0409] The compounds of the present invention can also be used in combination with antihypertensive agents. Any anti-hypertensive agent can be used as the second agent in such combinations. Examples of presently marketed products containing antihypertensive agents include calcium channel blockers, such as Cardizem, Adalat, Calan, Cardene, Covera, Dilacor, DynaCirc, Procardia XL, Sular, Tiazac, Vascor, Verelan, Isoptin, Nimotop, Norvasc, and Plendil; angiotensin converting enzyme (ACE) inhibitors, such as Accupril, Altace, Captopril, Lotensin, Mavik, Monopril, Prinivil, Univasc, Vasotec and Zestril.

[0410] Examples of compounds that may be used in combination with the compounds of the present invention to prevent or treat osteoporosis include: anti-resorptive agents including progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin, estrone, estriol or 17α- or 17β-ethynyl estradiol); progestins including algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogesterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, and tigestol; and bone resorption inhibiting polyphosphonates including polyphosphonates such as of the type disclosed in U.S. Pat. No. 3,683,080, the disclosure of which is incorporated herein by reference. Examples of polyphosphonates include geminal diphosphonates (also referred to as bis-phosphonates), tiludronate disodium, ibandronic acid, alendronate, resindronate zoledronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. Salts, co-crystals and esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-N,N-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic

acid, pentane-5-amino-1-hydroxy- -1,1-diphosphonic acid, and hexane-6-amino-1-hydroxy-1,1-diphosphonic acid.

[0411] Estrogen agonist/antagonist include 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, tamoxifen: (ethanamine, 2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and related compounds which are disclosed in U.S. Pat. No. 4,536,516, the disclosure of which is incorporated herein by reference, 4-hydroxy tamoxifen, which is disclosed in U.S. Pat. No. 4,623,660, the disclosure of which is incorporated herein by reference, raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)eth- oxy)phenyl)-hydrochloride) which is disclosed in U.S. Pat. No. 4,418,068, the disclosure of which is incorporated herein by reference, toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-- , (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. Pat. No. 4,996,225, the disclosure of which is incorporated herein by reference, centchroman: 1-(2-((4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-pyrrolidine, which is disclosed in U.S. Pat. No. 3,822,287, the disclosure of which is incorporated herein by reference, levormeloxifene, idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrolidinone, which is disclosed in U.S. Pat. No. 4,839,155, the disclosure of which is incorporated herein by reference, 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol which is disclosed in U.S. Pat. No. 5,488,058, the disclosure of which is incorporated herein by reference, 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol, which is disclosed in U.S. Pat. No. 5,484,795, the disclosure of which is incorporated herein by reference, (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc, TSE-424 (Wyeth-Ayerst Laboratories) and arazoxifene, cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-

5,6,7,8-te- trahydro-naphthalene-2-ol (also known as lasofoxifene); cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; cis-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydro-naphthalene-2-ol; 1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline, 2-phenyl-3-aroyl-benzothiophene and 2-phenyl-3-aroylbenzothiophene-1-oxide.

[0412] Other anti-osteoporosis agents, which can be used as the second agent in combination with a compound of the present invention, include, for example, the following: parathyroid hormone (PTH) (a bone anabolic agent); parathyroid hormone (PTH) secretagogues (see, e.g., U.S. Pat. No. 6,132,774), particularly calcium receptor antagonists; calcitonin; and vitamin D and vitamin D analogs. Further anti-osteoporosis agents includes a selective androgen receptor modulator (SARM). Examples of suitable SARMs include compounds such as cyproterone acetate, chlormadinone, flutamide, hydroxyflutamide, bicalutamide, nilutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g] quinoline derivatives, 1,2-dihydropyridino[5,6-g]quinoline derivatives and piperidino[3,2-g]quinolinone derivatives. Other examples include cypterone, also known as (1b,2b)-6-chloro-1,2-dihydro-17-hydroxy-3'-H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione is disclosed in U.S. Pat. No. 3,234,093. Chlormadinone, also known as 17-(acetyloxy)-6-chloropregna-4,6-diene-3,20-dione, in its acetate form, acts as an anti-androgen and is disclosed in U.S. Pat. No. 3,485,852. Nilutamide, also known as 5,5-dimethyl-3-[4-nito-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione and by the trade name Nilandron® is disclosed in U.S. Pat. No. 4,097,578. Flutamide, also known as 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide and the trade name Eulexin® is disclosed in U.S. Pat. No. 3,847,988. Bicalutamide, also known as 4'-cyano-a',a',a'-trifluo- ro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-m-toluidide and the trade name Casodex® is disclosed in EP-100172. The

enantiomers of biclutamide are discussed by Tucker and Chesterton, J. Med. Chem. 1988, 31, 885-887. Hydroxyflutamide, a known androgen receptor antagonist in most tissues, has been suggested to function as a SARM for effects on IL-6 production by osteoblasts as disclosed in Hofbauer et al. J. Bone Miner. Res. 1999, 14, 1330-1337. Additional SARMs have been disclosed in U.S. Pat. No. 6,017,924; WO 01/16108, WO 01/16133, WO 01/16139, WO 02/00617, WO 02/16310, U.S. Patent Application Publication No. US 2002/0099096, U.S. Patent Application Publication No. US 2003/0022868, WO 03/011302 and WO 03/011824. All of the above references are hereby incorporated by reference herein.

Formulations

[0413] Unit dose amounts and dose scheduling for the pharmaceutical compositions of the present invention can be determined using methods well known in the art. In one aspect, the compounds of the invention are administered orally in a total daily dose of about 0.375 μg/kg/day to about 3.75 mg/kg/day. In another aspect the total daily dose is from about 3.75 μg/kg/day to about 0.375 mg/kg/day. In another aspect the total daily dose is from about 3.75 μg/kg/day to about 37.5 μg/kg/day. In another aspect the total daily dose is from about 3.75 μg/kg/day to about 60 μg/kg/day. In a further aspect the dose range is from 30 μg/kg/day to 3.0 mg/kg/day. In one aspect, the compounds of the invention are administered orally in a unit dose of about 0.375 μg/kg to about 3.75 mg/kg. In another aspect the unit dose is from about 3.75 μg/kg to about 0.375 mg/kg. In another aspect the unit dose is from about 3.75 μg/kg to about 37.5 μg/kg. In another aspect the unit dose is from about 3.75 μg/kg to about 60 μg/kg. In one aspect, the compounds of the invention are administered orally in a unit dose of about 0.188 μg/kg to about 1.88 mg/kg. In another aspect the unit dose is from about 1.88 μg/kg to about 0.188 mg/kg. In another aspect the unit dose is from about 1.88 μg/kg to about 18.8 μg/kg. In another aspect the unit dose is from about 1.88 μg/kg to about 30 μg/kg. In one aspect, the compounds of the invention are administered orally in a unit dose of about 0.125 μg/kg to about 1.25 mg/kg.

In another aspect the unit dose is from about 1.25 μg/kg to about 0.125 mg/kg. In another aspect the unit dose is from about 1.25 μg/kg to about 12.5 μg/kg. In another aspect the unit dose is from about 1.25 μg/kg to about 20 μg/kg. In one embodiment the unit dose is administered once a day. In another embodiment the unit dose is administered twice a day. In another embodiment the unit dose is administered three times a day. In another embodiment the unit dose is administered four times a day.

[0414] Dose refers to the equivalent of the free acid. The use of controlled-release preparations to control the rate of release of the active ingredient may be preferred. The daily dose may be administered in multiple divided doses over the period of a day. Doses and dosing schedules may be adjusted to the form of the drug or form of delivery used. For example, different dosages and scheduling of doses may be used when the form of the drug is in a controlled release form or intravenous delivery is used with a liquid form.

[0415] Compounds of this invention when used in combination with other compounds or agents may be administered as a daily dose or an appropriate fraction of the daily dose (*e.g.*, bid). Administration of compounds of this invention may occur at or near the time in which the other compound or agent is administered or at a different time. When compounds of this invention are used in combination with other compounds or agents, the other compound or agent (*e.g.*, atorvastatin) may be administered at the approved dose or a lower dose.

[0416] For the purposes of this invention, the compounds may be administered by a variety of means including orally, parenterally, by inhalation including but not limited to nasal spray, topically, implantables or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intra-arterial injections with a variety of infusion techniques. Intra-arterial and intravenous injection as used herein includes administration through catheters. Oral administration is generally preferred.

[0417] Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, pellets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets and pellets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets and pellets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0418] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0419] Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*,

lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0420] Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0421] Dispersible powders, pellets, and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0422] The pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents.

[0423] Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[0424] In another aspect the pharmaceutical compositions may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0425] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain 0.2 to 2000 μmol (approximately 0.1 to 1000 mg) of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 99.9% of the total compositions. It is preferred that the pharmaceutical composition be prepared which provides easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion should contain from about 0.05 to about 500 μmol (approximately 0.025 to 250 mg) of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/h can occur.

[0426] As noted above, formulations suitable for oral administration may be presented as discrete units such as capsules, cachets, pellets, or tablets each

containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

[0427] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free flowing form such as a powder or granules, optionally mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach. This is particularly advantageous with the compounds of the present invention when such compounds are susceptible to acid hydrolysis.

[0428] Pharmaceutical compositions comprising the compounds of the present invention can be administered by controlled- or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to treat or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. (Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 Technomic Publishing, Lancaster, Pa.: 2000).

[0429] Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

[0430] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

[0431] A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These

dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized forms of compositions of the invention and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, DUOLITE A568 and DUOLITE AP143 (Rohm & Haas, Spring House, Pa. USA).

[0432] One embodiment of the invention encompasses a unit dosage form which comprises a compound of the present invention or a pharmaceutically acceptable salt, or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

[0433] A particular and well-known osmotic drug delivery system is referred to as OROS (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B 1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS Push-Pull, Delayed Push-Pull, Multi-Layer Push-Pull, and Push-Stick Systems, all of which are well known. Additional OROS systems that can be used for the controlled oral delivery of compounds and compositions of the invention include OROS-CT and L-OROS. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

[0434] Conventional OROS oral dosage forms are made by compressing a drug powder (e.g., a T3 mimetic composition of the present invention) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). (Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 Technomic Publishing, Lancaster, Pa. 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS drug delivery systems cannot be used to effectively deliver drugs with low water solubility.

[0435] A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a compound of the present invention, including a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

[0436] Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a

liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a compound of the present invention, including a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

[0437] Transdermal Delivery System: The controlled release formulations of the present invention may be formulated as a transdermal delivery system, such as transdermal patches. In certain embodiments of the present invention, a transdermal patch comprises a compound of the present invention contained in a reservoir or a matrix, and an adhesive which allows the transdermal device to adhere to the skin, allowing the passage of the active agent from the transdermal device through the skin of the patient. Once the compound has penetrated the skin layer, the drug is absorbed into the blood stream where it exerts desired pharmaceutical effects. The transdermal patch releases the compound of the present invention in a controlled-release manner, such that the blood levels of the a compound of the present invention is maintained at a therapeutically effective level through out the dosing period, and the blood levels of the a compound of the present invention is maintained at a concentration that is sufficient to reduce side effects associated with immediate release dosage forms but not sufficient to negate the therapeutic effectiveness of the compound.

[0438] Transdermal refers to the delivery of a compound by passage through the skin or mucosal tissue and into the blood stream. There are four main types of transdermal patches listed below.

[0439] Single-layer Drug-in-Adhesive: The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

[0440] Multi-layer Drug-in-Adhesive: The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

[0441] Reservoir: Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer.

[0442] Matrix: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

[0443] Other modes of transdermal delivery are known in the art and are included in the present invention.

[0444] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0445] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0446] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0447] Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-

aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0448] In one aspect the unit dosage formulations are those containing a daily dose or unit, daily sub-dose, or an appropriate fraction thereof, of a drug.

[0449] It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

Synthesis of Compounds of Formula I, II, III, VIII, XVI, and XVII

[0450] The compounds in this invention may be prepared by the processes described in the following Schemes, as well as relevant published literature procedures that are used by those skilled in the art. It should be understood that the following schemes are provided solely for the purpose of illustration and do not limit the invention which is defined by the claims. Typically the synthesis of a compound of Formula I, II, III, VIII, XVI, and XVII includes the following general steps: (1) Preparation of a phosphonate prodrug; (2) Deprotection of a phosphonate ester; (3) Introduction of a phosphonate group; (4) Construction of the diaryl ring system; and (5) Preparation of key precursors. The order of introduction of a phosphonate group and the construction of the diaryl backbone in the synthesis of compounds of Formula I, II, III, VIII, XVI, and XVII can be freely decided by those skilled in the art based on the structure of the substrate. In all applicable structures contained in the Schemes described in this invention, PG refers to a protecting group and

FG refers to a functional group that can be transformed into T. Protection and deprotection in the Schemes may be carried out according to the procedures generally known in the art (*e.g.*, "Protecting Groups in Organic Synthesis", 3rd Edition, Wiley, 1999).

[0451] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have stereogenic centers at the phosphorus atom and at any of the carbons including any of the R substituents. Consequently, compounds of Formula I, II, III, VIII, XVI, and XVII can exist in enantiomeric or diastereomeric forms or in mixture thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Preparation of A Phosphonate Prodrug

[0452] Prodrugs can be introduced at different stages of the synthesis. Most often these prodrugs are made from the phosphonic acids of Formula I because of their lability.

[0453] Phosphonic acids of Formula I can be alkylated with electrophiles such as alkyl halides and alkyl sulfonates under nucleophilic substitution conditions to give phosphonate esters. For example, compounds of Formula I wherein YR^{11} is an acyloxyalkyl group can be prepared by direct alkylation of compounds of Formula I with an appropriate acyloxyalkyl halide (*e.g.*, Cl, Br, I; *Phosphorus Sulfur 54*:143 (1990); *Synthesis* 62 (1988)) in the presence of a suitable base (*e.g.*, pyridine, TEA, diisopropylethylamine) in suitable solvents such as DMF (*J. Med. Chem. 37*:1875 (1994)). The carboxylate component of these acyloxyalkyl halides includes but is not limited to acetate, propionate, isobutyrate, pivalate, benzoate, carbonate and other carboxylates.

[0454] Dimethylformamide dialkyl acetals can also be used for the alkylation of phosphonic acids (*Collect. Czech Chem. Commu. 59*:1853 (1994)). Compounds of Formula I wherein YR^{11} is a cyclic carbonate, a lactone or a

phthalidyl group can also be synthesized by direct alkylation of the free phosphonic acids with appropriate halides in the presence of a suitable base such as NaH or diisopropylethylamine (*J. Med. Chem. 38*:1372 (1995); *J. Med. Chem. 37*:1857 (1994); *J. Pharm. Sci. 76*:180 (1987)).

[0455] Alternatively, these phosphonate prodrugs can be synthesized by the reactions of the corresponding dichlorophosphonates and an alcohol (*Collect Czech Chem. Commun. 59*:1853 (1994)). For example, a dichlorophosphonate is reacted with substituted phenols and arylalkyl alcohols in the presence of a base such as pyridine or TEA to give the compounds of Formula I wherein YR^{11} is an aryl group (*J. Med. Chem. 39*:4109 (1996); *J. Med. Chem. 38*:1372 (1995); *J. Med. Chem. 37*:498 (1994)) or an arylalkyl group (*J. Chem. Soc. Perkin Trans. 1 38*:2345 (1992)). The disulfide-containing prodrugs (*Antiviral Res. 22*:155 (1993)) can be prepared from a dichlorophosphonate and 2-hydroxyethyldisulfide under standard conditions. Dichlorophosphonates are also useful for the preparation of various phosphonamides as prodrugs. For example, treatment of a dichlorophosphonate with ammonia gives both a monophosphonamide and a diphosphonamide; treatment of a dichlorophosphonate with 1-amino-3-propanol gives a cyclic 1,3-propylphosphonamide; treatment of a chlorophosphonate monophenyl ester with an amino acid ester in the presence of a suitable base gives a substituted monophenyl monophosphonamidate.

[0456] Such reactive dichlorophosphonates can be generated from the corresponding phosphonic acids with a chlorinating agent (*e.g.*, thionyl chloride, *J. Med. Chem.* 1857 (1994); oxalyl chloride, *Tetrahedron Lett. 31*:3261 (1990); phosphorous pentachloride, *Synthesis* 490 (1974)). Alternatively, a dichlorophosphonate can be generated from its corresponding disilyl phosphonate esters (*Synth. Commu. 17*:1071 (1987)) or dialkyl phosphonate esters (*Tetrahedron Lett. 24*:4405 (1983); *Bull. Soc. Chim. 130*:485 (1993)).

[0457] It is envisioned that compounds of Formula I can be mixed phosphonate ester (*e.g.*, phenyl and benzyl esters, or phenyl and acyloxyalkyl

esters) including the chemically combined mixed esters such as phenyl and benzyl combined prodrugs reported in *Bioorg. Med. Chem. Lett. 7*:99 (1997).

[0458] Dichlorophosphonates are also useful for the preparation of various phosphonamides as prodrugs. For example, treatment of a dichlorophosphonate with an amine (*e.g.* an amino acid alkyl ester such as L-alanine ethyl ester) in the presence of a suitable base (*e.g.* triethylamine, pyridine, etc.) gives the corresponding bisphosphonamide; treatment of a dichlorophosphonate with 1-amino-3-propanol gives a cyclic 1,3-propylphosphonamide; treatment of a chlorophosphonate monophenyl ester with an amino acid ester in the presence of a suitable base gives a substituted monophenyl monophosphonamidate. Direct couplings of a phosphonic acid with an amine (*e.g.* an amino acid alkyl ester such as L-alanine ethyl ester) are also reported to give the corresponding bisamidates under Mukaiyama conditions (*J. Am. Chem. Soc., 94*:8528 (1972)).

[0459] The SATE (*S*-acetyl thioethyl) prodrugs can be synthesized by the coupling reaction of the phosphonic acids of Formula I and S-acyl-2-thioethanol in the presence of DCC, EDCI or PyBOP (*J. Med. Chem. 39*:1981 (1996)).

[0460] Cyclic phosphonate esters of substituted 1,3-propane diols can be synthesized by either reactions of the corresponding dichlorophosphonate with a substituted 1,3-propanediol or coupling reactions using suitable coupling reagents (*e.g.*, DCC, EDCI, PyBOP; *Synthesis* 62 (1988)). The reactive dichlorophosphonate intermediates can be prepared from the corresponding acids and chlorinating agents such as thionyl chloride (*J. Med. Chem.* 1857 (1994)), oxalyl chloride (*Tetrahedron Lett. 31*:3261 (1990)) and phosphorus pentachloride (*Synthesis* 490 (1974)). Alternatively, these dichlorophosphonates can also be generated from disilyl esters (*Synth. Commun. 17*:1071 (1987)) and dialkyl esters (*Tetrahedron Lett. 24*:4405 (1983); *Bull. Soc. Chim. Fr., 130*:485 (1993)).

[0461] Alternatively, these cyclic phosphonate esters of substituted 1,3-propane diols are prepared from phosphonic acids by coupling with diols under Mitsunobu reaction conditions (*Synthesis* 1 (1981); *J.Org. Chem.*

52:6331 (1992)), and other acid coupling reagents including, but not limited to, carbodiimides (*Collect. Czech. Chem. Commun.* 59:1853 (1994); *Bioorg. Med. Chem. Lett.* 2:145 (1992); *Tetrahedron Lett.* 29:1189 (1988)), and benzotriazolyloxytris-(dimethylamino) phosphonium salts (*Tetrahedron Lett.* 34:6743 (1993)).

[0462] Phosphonic acids also undergo cyclic prodrug formation with cyclic acetals or cyclic *ortho* esters of substituted propane-1,3-diols to provide prodrugs as in the case of carboxylic acid esters (*Helv. Chim. Acta.* 48:1746 (1965)). Alternatively, more reactive cyclic sulfites or sulfates are also suitable coupling precursors to react with phosphonic acid salts. These precursors can be made from the corresponding diols as described in the literature.

[0463] Alternatively, cyclic phosphonate esters of substituted 1,3-propane diols can be synthesized by *trans* esterification reaction with substituted 1,3-propane diol under suitable conditions. Mixed anhydrides of parent phosphonic acids generated *in situ* under appropriate conditions react with diols to give prodrugs as in the case of carboxylic acid esters (*Bull. Chem. Soc. Jpn.* 52:1989 (1979)). Aryl esters of phosphonates are also known to undergo transesterification with alkoxy intermediates (*Tetrahedron Lett.* 38:2597 (1997); *Synthesis* 968 (1993)).

[0464] One aspect of the present invention provides methods to synthesize and isolate single isomers of prodrugs of phosphonic acids of Formula I, II, III, VIII, XVI, and XVII. Because phosphorus is a stereogenic atom, formation of a prodrug with a racemic substituted-1,3-propane-diol will produce a mixture of isomers. For example, formation of a prodrug with a racemic 1-(V)-substituted-1,3-propane diol gives a racemic mixture of cis-prodrugs and a racemic mixture of trans-prodrugs. In an other aspect, the use of the enantioenriched substituted-1,3-propane diol with the R-configuration gives enantioenriched R-cis-and R-trans-prodrugs. These compounds can be separated by a combination of column chromatography and/or fractional crystallization.

A. Deprotection of A Phosphonate Ester

[0465] Compounds of Formula I, II, III, VIII, and XVII wherein X is $-PO_3H_2$ may be prepared from phosphonate esters using the known cleavage methods. Silyl halides are generally used to cleave various phosphonate esters and give the desired phosphonic acid upon mild hydrolysis of the resulting silyl phosphonate esters. When needed, acid scavengers (for example, HMDS) can be used for the acid sensitive compounds. Such silyl halides include TMSCl (*J. Org. Chem. 28*:2975 (1963)), TMSBr (*Tetrahedron Lett.* 155 (1977)) and TMSI (*J. Chem. Soc., Chem. Commu.* 870 (1978)). Alternatively, phosphonate esters can be cleaved under strong acid conditions (*Tetrahedron Lett. 33*:4137 (1992); *Synthesis-Stuttgart 10*:955 (1993)). Those phosphonate esters can also be cleaved via dichlorophosphonates prepared by treating the phosphonate esters with halogenating agents such as PCl_5, $SOCl_2$ and BF_3 (*J. Chem. Soc.* 238 (1961)) followed by aqueous hydrolysis to give the phosphonic acids. Aryl and benzyl phosphonate esters can be cleaved under hydrogenolysis conditions (*Synthesis* 412 (1982); *J. Med. Chem. 28*1208 (1985)) or metal reduction conditions (*J. Chem. Soc. 99*:5118 (1977)). Electrochemical (*J. Org. Chem. 44*:4508 (1979)) and pyrolysis (*Synth. Commu. 10*:299 (1980)) conditions have been used to cleave various phosphonate esters.

Introduction of A Phosphonate Group

[0466] The introduction of a phosphonate group can generally be accomplished according to known methods. Compounds of Formula I, III, VIII, and XVII wherein T is $-O(CR^b_2)(CR^a_2)_n-$, $-S(CR^b_2)(CR^a_2)_n-$ or $-N(R^c)(CR^b_2)(CR^a_2)_n-$ may be prepared by coupling a phenol, thiophenol, or aniline with a phosphonate ester component such as $I(CR^b_2)(CR^a_2)_nP(O)(OEt)_2$, $TsO(CR^b_2)(CR^a_2)_nP(O)(OEt)_2$, or $TfO(CR^b_2)(CR^a_2)_nP(O)(OEt)_2$ in the presence of a base such as NaH, K_2CO_3, KO-t-Bu or TEA (*Tetrahedron Lett. 27*:1477 (1986); *J. Chem. Soc. Perkin Tran 1* 1987 (1994)) as described in Scheme 1. Following the procedures

described as above, deprotection of the phosphonate ester **2** gives the desired phosphonic acid **3**.

[0467] Compounds of Formula I, III, VIII, and XVII wherein T is $-N(R^b)C(O)(CR^a_2)_n-$ can be prepared by coupling an aniline **1** (M = NH) with a carboxylic acid containing a phosphonate moiety $(EtO)_2P(O)(CR^a_2)_{1-2}CO_2H$ in the presence of DCC or EDC according to the known methods (for example, *J. Org. Chem. 42*:2019 (1977)) or converting an aniline **1** (M = NH) to an isocyanate with diphosgene followed by reacting with $P(OEt)_3$ (*J. Org. Chem.* 1661 (1956); *Tetrahedron Lett. 37*:5861 (1996)). Deprotection of the phosphonate ester **2** as described above leads to the phosphonic acid **3**.

[0468] For compounds of Formula I, III, VIII, and XVII wherein T is $-(CR^a_2)_k-$, the phosphonate group can be introduced by a number of known methods. For example, the coupling reaction of a phenyl bromide (*J. Org. Chem. 64*:120 (1999)), iodide (*Phosphorus Sulfur 130*:59 (1997)) or triflate (*J. Org. Chem. 66*:348 (2001)) with diethyl phosphonate in the presence of a Pd catalyst is widely used within the art (when k is 0). Other methods such as Michaelis-Arbuzov reaction (*Chem. Rev. 81*:415 (1981)) can also be an efficient way to introduce the phosphonate group by coupling a benzyl or arylalkyl halide with triethyl phosphonate (when m is 1-3).

[0469] For compounds of Formula I, III, VIII, and XVII wherein T is $-(CR^a_2)_n-CR^b=CR^b-$, the phosphonate group can be introduced by coupling an aldehyde and tetraethyl methylenediphosphonate in the presence of a base such as NaH, NaOH or KO-t-Bu (*Tetrahedron Lett. 29*:3007 (1988)). For compounds of Formula I, II, III, V, VI, and VII wherein T is $-CR^b=CR^b-(CR^a_2)_n-$ or $-(CR^a_2)-CR^b=CR^b-(CR^a_2)-$, the phosphonate group can be introduced by Michaelis-Arbuzov reaction of the corresponding olefinic halide with triethyl phosphite.

[0470] For compounds of Formula I, III, VIII, and XVII wherein T is $-(CR^a_2)_m(CO)-$, the phosphonate group can be introduced by reacting diethyl phosphite with an acid chloride (*J. Org. Chem. 29*:3862 (1964); *Tetrahedron 54*:12233 (1998)) or an aldehyde followed by oxidation (*Tetrahedron 52*:9963 (1996)). Also, this type of compounds can be transformed into the compounds

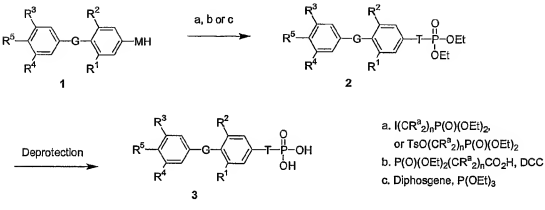
of Formula I, III, VIII, and XVII wherein T is -$(CR^a_2)_nCH(NR^bR^c)$- according to known procedures (*Tetrahedron Lett. 37*:407 (1996)).

[0471] For compounds of Formula I, III, VIII, and XVII wherein T is -$(CO)(CR^a_2)_m$-, the phosphonate group can be introduced by a number of known methods such as reacting a substituted benzoyl chloride with diethylphosphonoacetic acid (*Synthetic Commu. 30*:609 (2000)) or a phosphonate copper reagent (*Tetrahedron Lett. 31*:1833 (1990)). Alternatively, coupling of triethyl phosphonate with a silyl enol ether (*Synthetic Commu. 24*:629 (1994)) or a α-bromobenzophenone (*Phosphorus Sulfur 90*:47 (1994)) can also introduce the phosphonate group.

[0472] For compounds of Formula I, III, VIII, and XVII wherein T is -$C(O)NH(CR^b_2)(CR^a_2)_p$-, the phosphonate group can be introduced by coupling reaction of a substituted benzoic acid and an aminophosphonate according to the standard amide bond formation methods (*Tetrahedron Lett. 31*:7119 (1990); *Tetrahedron Lett. 30*:6917 (1989); *J. Org. Chem. 58*:618 (1993)).

[0473] For compounds of Formula I, III, VIII, and XVII wherein T is -$(CR^a_2)C(O)(CR^a_2)_n$- or $(CR^a_2)_nC(O)(CR^a_2)$, the phosphonate group can be introduced by reacting a benzyl bromide with a functionalized phosphonate (*Tetrahedron Lett. 30*:4787 (1989)). Alternatively, a coupling reaction of a substituted phenylacetate and methylphosphonate also yields the desired product (*J. Am. Chem. Soc. 121*:1990 (1999)).

Scheme 1



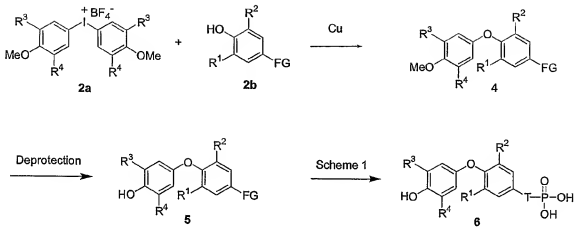
M = O, S, NH

T = O(CR$^a_2$)$_n$, S(CR$^a_2$)$_n$, NR^b(CR$^a_2$)$_n$, NR^b(CO)(CR$^a_2$)$_n$

Construction of The Diaryl Ring

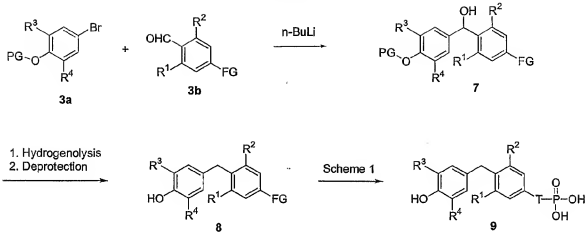
[0474] Compounds of Formula I, II, VIII, XVI, and XVII wherein G is –O- can be prepared according to known methods. As described in Scheme 2, **2a** is reacted with **2b** at room temperature in the presence of Cu powder and a suitable base such as TEA, diisopropylamine or pyridine to provide the coupling product **4** (*J. Med. Chem. 38*:695 (1995)). Deprotection of the methoxy group with suitable reagents such as boron tribromide, boron trichloride or boron trifluoride in CH_2Cl_2 gives the intermediate **5**. Introduction of the phosphonate group followed by deprotection of the phosphonate ester as described in Scheme 1 leads to the desired phosphonic acid **6**. Those skilled in the art can use other known methods such as coupling of an arylboronic acid and a phenol in the presence of $Cu(OAc)_2$ (*Tetrahedron Lett. 39*:2937 (1998)), nucleophilic substitution of a fluorobenzene (*Synthesis-Stuttgart 1*:63 (1991)) or iodobenzene (*J. Am. Chem. Soc. 119*:10539 (1997)) with a phenol and coupling of a bromobenzene with a phenol in the presence of $Pd_2(dba)_3$ (*Tetrahedron Lett. 38*:8005 (1997)) to form the diaryl ether system.

Scheme 2



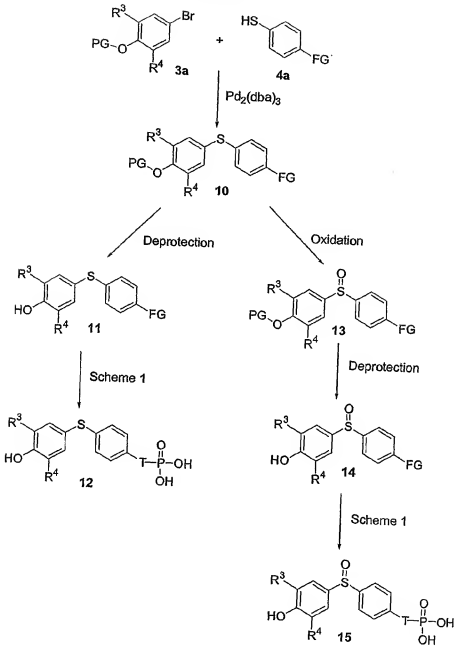
[0475] For compounds of Formula I, II, VIII, XVI, and XVII wherein G is $-CH_2-$, the installation of the diaryl ring can be accomplished by a number of known methods. For example, as described in Scheme 3, benzyl alcohol **7** is formed by treatment of **3a** with n-BuLi at –78 °C in THF followed by reacting with **3b** (*Bioorg. Med. Chem. Lett. 10*:2607 (2000)). Hydrogenolysis with Pd-C or dehydroxylation of benzyl alcohol **7** by $NaBH_4$ (*Synthetic Commu. 17*:1001 (1987)) and $(i\text{-}Bu)_3Al$ (*Synthesis* 736 (1987)) followed by removal of the protecting group gives the diaryl intermediate **8**. Phosphonic acid **9** is formed from **8** according to the same procedures as described in Scheme 1. Alternatively, coupling of benzyl bromide with an aryl Grignard reagent (*Tetrahedron Lett. 22*:2715 (1981)), an arylboronic acid (*Tetrahedron, Lett. 40*:7599 (1999)) or a zinc reagent (*Chem. Lett. 11*:1241 (1999)) and reduction of a diaryl ketone (*J. Org. Chem. 51*:3038 (1986)) are all widely used methods for the construction of the diaryl ring.

Scheme 3



[0476] For compounds of Formula I, II, VIII, XVI, and XVII wherein G is –S-, -S(=O)- or -S(=O_2)-, the formation of the diaryl ring can be achieved according to known methods. As illustrated in Scheme 4, **3a** can be reacted with **4a** in the presence of a catalyst such as $Pd_2(dba)_3$ or CuBr to provide the diaryl sulfide **10** (*Tetrahedron 57*:3069 (2001); *Tetrahedron Lett. 41*:1283 (2000)). Phosphonic acid **12** is formed from **10** after removal of the protecting groups followed by the same procedures as described in Scheme 1. The diaryl sulfide **10** can also be converted to the sulfoxide **13** according to known methods (*Synthetic Commu. 16*:1207 (1986); *J. Org. Chem. 62*:4253 (1997); *Tetrahedron Lett. 31*:4533 (1990)), which leads to the phosphonic acid **15** following the same procedures as described in Scheme 1. Also, the biaryl sulfide **10** can be converted to the sulfone (*Tetrahedron Lett. 32*:7353 (1991); *J. Prakt. Chem.* 160 (1942)) which leads to the phosphonic acid (G is -S(=O_2)-) following the same procedures as described above. In addition, nucleophilic substitution of chlorobenzene and bromobenzene with a thiol is also an efficient way to install the diaryl sulfide ring (*J. Med. Chem. 31*:254 (1988); *J. Org. Chem. 63*:6338 (1998)).

Scheme 4

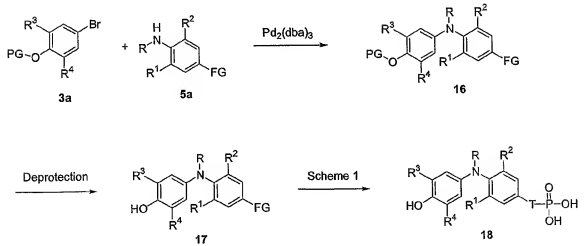


PG = protecting group
FG = functional group that can be transformed into T

[0477] For compounds of Formula I, II, VIII, XVI, and XVII wherein G is –NH- or –N(C_1-C_4 alkyl)-, the diarylamine backbone can be formed by a

number of known methods. Among those conditions, one widely used by those skilled in the art is the coupling reaction of an aniline with an aryl bromide (*J. Org. Chem. 64*:5575 (1999); *J. Org. Chem. 62*:6066 (1997); *Tetrahedron Lett. 37*:6993 (1996); *Org. Lett. 1*:2057 (1999)) or an aryl tosylate (*J. Org. Chem. 62*:1268 (1997)) in the presence of a catalyst such as $PdCl_2$ or $Pd_2(dba)_3$. As illustrated in Scheme 5, the diarylamine intermediate **16** can be prepared by coupling of bromide **3a** and aniline **5a** in the presence of $Pd_2(dba)_3$. After removal of the protecting group, the diarylamine **17** is converted to the phosphonic acid **18** following the same procedures as described in Scheme 1. Alternatively, coupling of an aniline and aryl halide using other catalysts such as copper-bronze (*Org. Synth. 2*:446 (1943); *J. Org. Chem.* 20 (1955)) and $Cu(OAc)_2$ (*J. Med. Chem. 4*:470 (1986); *Synthetic Commu. 26*:3877 (1996)) to construct the diarylamine backbone is also a feasible approach.

Scheme 5

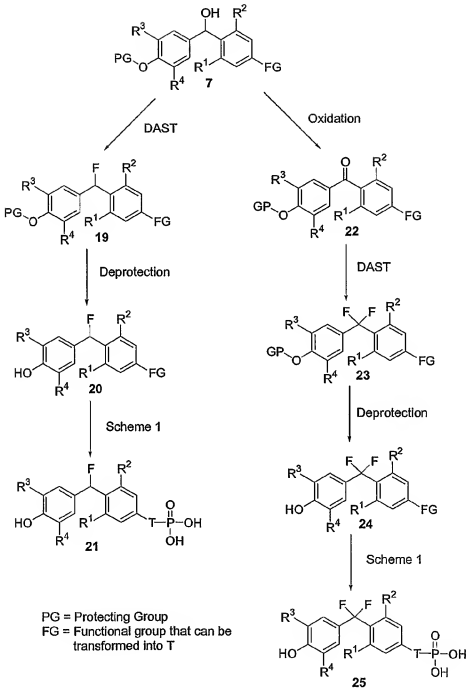


R = H, C_1-C_4 alkyl
PG = Protecting Group
FG = Functional group that can be transformed into T

[0478] For compounds of Formula I, II, VIII, XVI, and XVII wherein G is –CHF- or -CF_2-, the diaryl backbone can be established from the benzyl alcohol **7**. Accordingly, as described in Scheme 6, benzyl alcohol **7** can be

converted to the benzyl fluoride **19** by reacting with DAST in CH_2Cl_2 according to known procedures (*J. Chem. Soc., Chem. Commu. 11*:511 (1981); *Tetrahedron Lett. 36*:6271 (1995); *Tetrahedron 14*:2875 (1988)). Also, the benzyl alcohol **7** can be easily oxidized to the benzophenone **22** according to known methods such as MnO_2 oxidation, PCC oxidation, Swern oxidation and Dess-Martin oxidation, which is subsequently converted to the benzyl difluoride **23** by treatment with DAST (*J. Fluorine 61*:117 (1993)) or other known reagents (*J. Org. Chem. 51*:3508 (1986); *Tetrahedron 55*:1881 (1999)). After removal of the protecting groups, the benzyl fluoride **20** and difluoride **24** are converted to the desired phosphonic acids following the same procedures as described in Scheme 1.

Scheme 6



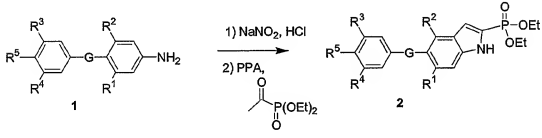
[0479] Compounds of Formula I, II, VIII, XVI, and XVII wherein G is -CH(OH)- or -C(O)- can be prepared from the intermediates **7** and **22**. Removal of the protecting groups of **7** and **22** followed by introduction of the

phosphate and deprotection as described in Scheme 1 provides the desired phosphonic acids of Formula I.

Synthesis of compounds of Formula II

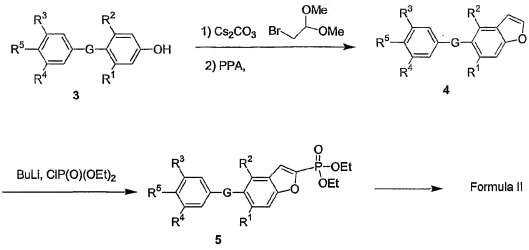
[0480] The synthesis of compounds of Formula II where A is –NH- and B is –CH- or -C-alkyl- can be accomplished from the corresponding amino diaryl precursor **1** using the well-known, to those skilled in the art, Fisher indole synthesis (Scheme 6a) (*Phosphorus and Sulfur* 37:41-63 (1988)). Alternatively, the aryl-indole scaffold is constructed using the procedures previously described and the phosphonic acid moiety is introduced by making the anion next to the nitrogen of the indole derivative, protected at the nitrogen, with a base such as BuLi and quenching the anion with diethyl chlorophosphate. Further protecting group and functional group manipulations of intermediates **2** provide compounds of Formula II.

Scheme 6a



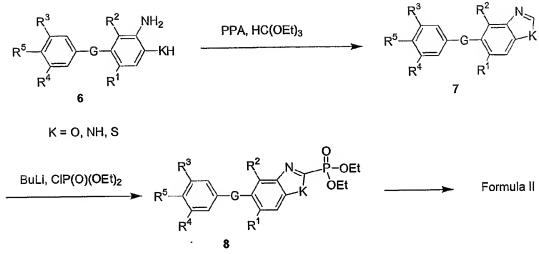
[0481] Compounds of Formula II where A is –O- and B is –CH- are synthesized from the corresponding diaryl phenol precursor **3** and ring cyclization with the dimethylacetal of bromoacetaldehyde to give benzofuran **4** (Scheme 6b) (*J. Chem. Soc., Perkin Trans. 1*, 4:729 (1984)). The phosphonic acid moiety can then be introduced by making the anion next to the oxygen of the benzofuran with a base such as BuLi and quenching the anion with diethyl chlorophosphate to provide phosphonate **5**. Further protecting group and functional group manipulations of intermediate **5** provides compounds of Formula II.

Scheme 6b



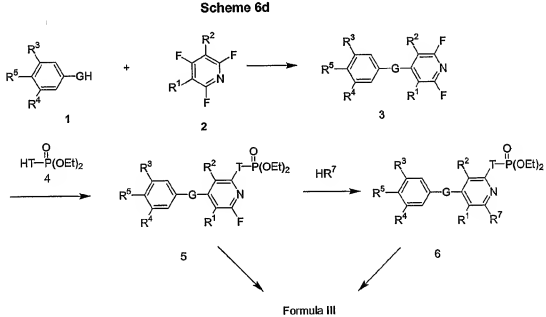
[0482] Compounds of Formula II where A is –NH-, -O- or –S- and B is –N- can be made from condensation of the corresponding diaryl precursor **6** with an orthoformate such as triethyl orthoformate in presence of acid to give heterocycle **7** (*Org. Prep. Proced. Int., 22(5)*:613-618 (1990)). The phosphonic acid moiety can then be introduced by making the anion at the 2-position of the heterocycle **7** with a base such as BuLi and quenching the anion with diethyl chlorophosphate to give phosphonate **8**. Further protecting group and functional group manipulations of intermediates **8** provide compounds of Formula II.

Scheme 6c



Synthesis of compounds of Formula III

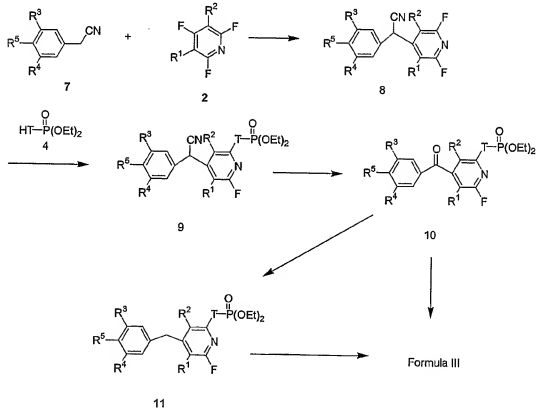
Scheme 6d



[0483] The general synthesis of compounds of Formula III wherein G is –O-, -S- or –NH- utilizes the displacement of an appropriately substituted phenol, thiophenol or aniline **1** with a pentasubstituted pyridine such as 3,5-dichloro-2,4,6-trifluoro-pyridine **2** to provide intermediate **3** (Scheme 6d) (*Org. Prep.*

Proced. Int. 32(5):502-504 (2000)). Subsequent displacement of the 2-fluoro and 6-fluoro substituents on the pyridine ring with nucleophiles **4** and HR^7 sequentially provide intermediates **5** and **6**. Examples of suitable nucleophiles, include but are not limited to, diethyl hydroxymethyl-phosphonate and diethyl aminomethyl-phosphonate. Example of reactants HR^7, include but are not limited to, alkylthiol, sodium alkoxide, alkylamine or benzylamine. Compounds of Formula III where G is -S(=O)- and -$S(=O)_2$- can be derived from intermediates **5** and **6** when G is –S- via oxidation with an oxidizing agent such as mCPBA. Further protecting group and functional group manipulations of intermediates **5** and **6** will provide compounds of Formula III.

Scheme 6e



[0484] Compounds of Formula III wherein G is $–CH_2$- or –C(O)- are synthesized according to scheme 6e. Condensation of benzyl cyanide **7** with

pentasubstituted pyridine **2** provide intermediate **8**. Displacement of 2-fluoro with reagent **4** gives intermediate **9**. Oxidation of benzyl cyanide **9** provides keto derivative **10** which after deprotection and functional group manipulation gives a compound of Formula III. Alternatively, reductive deoxygenation of keto intermediate followed by deprotection and functional group manipulation gives a compound of Formula III.

Synthesis of phosphonic acid monoesters

[0485] Compound of the invention where the acidic group is a phosphonic acid monoester may be prepared from the diester intermediate, used for the synthesis of phosphonic acid thyromimetic, by monosaponification. Monohydrolysis of one of the ester groups on the phosphonate may be accomplished by treatment of phosphonate diesters with aqueous alkaline solution such as NaOH, KOH or LiOH at rt or while heating. Sodium azide can also be used in DMF (*Bioorg. Med. Chem. Lett. 14(13)*,3559-62 (2004)) to accomplished the monosaponification. Alternatively, organic bases such as morpholine or N-methyl-piperazine can be used to hydrolyze one of the phosphonate ester groups (*Synth. Comm. 34(2)*:331-344 (2004)).

Synthesis of phosphinic acids

[0486] The introduction of a phosphinic acid group can generally be accomplished according to known methods. An efficient way to synthesize phosphinic acid is to convert a phosphonate diester to its corresponding monochloridate-monoester using one of many chlorinating agents such as PCl_5 (*Can. J. Chem. 76(3)*:313-18 (1998)), oxalyl chloride (*Tetrahedron Lett. 44(12)*:1445-48 (2003)), thionyl chloride (*J. Med. Chem. 45(4)*:919-29 (2002)) or phosgene (*Recl. Trav. Chim. Pays-Bas 78*:59-61 (1959)) and to introduce the carbon-based substituent on the phosphorus atom via a Grignard reagent (*J. Chem. Soc. Perkin Trans. 1 17*:2179-86 (1996)), a lithium anion (*J. Med. Chem. 33(11)*:2952-56 (1990)) or an enolate (*Bioorg Med. Chem. 5(7)*:1327-38 (1997)) to produce the desired phosphinate ester. The phosphinic acid is then generated by saponification with aqueous NaOH, KOH

or LiOH or using one of the many methods known to deprotect phosphonic acids such as TMSBr or TMSCl/KI. Alternatively, phosphinic acids can be generated from phosphonic acid monoesters by making the monochloridate-monoester with chlorinating reagents such as thionyl chloride or oxalyl chloride, and introducing the substituent on the phosphorus as above.

[0487] Compounds of Formula I wherein T is $-O(CR^b_2)(CR^a_2)_n-$, $-S(CR^b_2)(CR^a_2)_n-$ or $-N(R^c)(CR^b_2)(CR^a_2)_n-$ may be prepared by coupling a phenol, thiophenol, or aniline with a phosphinate ester component such as $I(CR^b_2)(CR^a_2)_nP(O)(OEt)$(lower alkyl), $TsO(CR^b_2)(CR^a_2)_nP(O)(OEt)$(lower alkyl), or $TfO(CR^b_2)(CR^a_2)_nP(O)(OEt)$(lower alkyl) in the presence of a base such as NaH, K_2CO_3, Cs_2CO_3, KO-t-Bu or TEA (*J. Am. Chem. Soc. 114(19)*:7604-06 (1992)). These phosphinate ester components can be synthesized by condensation of a mono phosphinate, such as ethyl methylphosphinate, with formaldehyde in presence of a base such Et_3N (*Tetrahedron Asymmetry 13(7)*:735-38 (2002)).

[0488] Compounds of Formula I wherein T is $-N(R^b)C(O)(CR^a_2)_n-$ can be prepared by coupling an aniline with a carboxylic acid containing a phosphinate moiety (lower alkyl)$(EtO)P(O)(CR^a_2)_{1-2}CO_2H$ in the presence of DCC or EDC according to the known methods (*Syn. Lett. 9*:1471-74 (2002)) or converting an aniline to a phenyl isocyanate with diphosgene followed by reacting with a mono-substituted phosphinate (*Zh. Obshch. Khim. 26*:3110-11 (1956)). Alternatively, condensation of the carbon anion of a phosphinate provides the β-amido-phosphinate (*J. Org. Chem. 45(12)*:2519-22 (1980)).

[0489] For compounds of Formula I wherein T is $-(CR^a_2)_k-$, the phosphonate group can be introduced by a number of known methods. For example, the coupling reaction of a phenyl halide (*Synthesis, 14*:2216-20 (2003)) with mono-substituted phosphinate in the presence of a Pd catalyst is widely used within the art (when k is 0). Other methods such as Michaelis-Arbuzov can also be an efficient way to introduce the phosphinate group by coupling a benzyl or arylalkyl halide with a phosphonite diester (when m is 1-3) (*Org. Lett. 5(17)*:3053-56 (2003)). Alternatively, phosphinates can be synthesized by coupling of mono-substituted phosphinate esters with olefins, such as

styrenes, in the presence of t-Bu_2O_2 (*Justus Liebig Ann. Chem.* 741-50 (1974)) or $(PhCO)_2O_2$ (*J. Gen. Chem. USSR 30*:2328-32 (1960)).

[0490] For compounds of Formula I wherein T is $-(CR^a_2)_n-CR^b=CR^b-$, the phosphonate group can be introduced by coupling an acetylene and a monosubstituted phosphinate in the presence of a catalyst such as $Ni(PPh_2Me)$, $Ni(cod)_2$ (*J. Am. Chem. Soc. 126(16)*:5080-81 (2004)) or $Me_2Pd(PPh_2)_2$ (*J. Am. Chem. Soc. 124(15)*:3842-43 (2002)). For compounds of Formula I wherein T is $-CR^b=CR^b-(CR^a_2)_n-$ or $-(CR^a_2)-CR^b=CR^b-(CR^a_2)-$, the phosphinate group can be introduced by Michaelis-Arbuzov reaction of the corresponding olefinic halide with a phosphonite diester.

[0491] For compounds of Formula I wherein T is $-(CR^a_2)_m(CO)-$, the phosphinate group can be introduced by reacting a phosphonite diester with an acyl chloride in the presence of sodium (*J. Gen. Chem. USSR 34*:4007-9 (1964)) or an aldehyde in the presence of lithium phenoxide followed by an oxidation (*Tetrahedron Lett. 45(36)*:6713-16 (2004)). Alternatively, treatment of an acyl chloride with a phosphonate diester provides access to α-keto-phosphinate (*J. Chem. Soc. Perkin Trans. 1*, 659-66 (1990)).

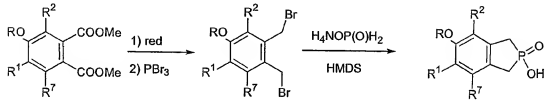
[0492] For compounds of Formula I wherein T is $-(CO)(CR^a_2)_m-$, the phosphinate group can be introduced by a number of known methods such as reacting a substituted benzoate ester with the anion of a phosphinate made with a base such as BuLi or LDA (*Bull. Soc. Chim. Fr.* 3494-3502 (1972)). Alternatively, coupling the anion of a phosphinate with a substituted benzaldehyde followed by an oxidation provides access to the β-keto-phosphinate (*J. Med. Chem. 38(17)*:3297-3312 (1995)).

[0493] For compounds of Formula I wherein T is $-C(O)NH(CR^b_2)(CR^a_2)_p-$, the phosphonate group can be introduced by a coupling reaction of an aminophosphinate (*Synthesis* 1074-76 (1995)) with substituted benzoyl chloride (*J. Organomet. Chem. 178*:157-69 (1979)) or a substituted benzoic acid according to the standard amide bond formation methods (*Bioorg. Med. Chem. Lett.* 6(14):1629-34 (1996)).

[0494] For compounds of Formula I wherein T is $-(CR^a_2)C(O)(CR^a_2)_n-$, the phosphinate group can be introduced by reacting a substituted phenylacetate

with a functionalized anion of a phosphinate made with a base such as BuLi or LDA (*Bull. Soc. Chim. Fr.* 3494-3502 (1972)).

Synthesis of cyclic phosphinic acids and cyclic phosphonic acids



[0495] Cyclic phosphinic acids can be synthesized starting from a 1,2-dicarboxylate-benzene precursor (*J. Am. Chem. Soc. 101*:7001-08 (1979)) which is reduced to the di-benzylic alcohol and brominated with PBr_3 to give the di-benzylic bromide precursor (*Synth. Commun. 14(6)*:507-514 (1984)). Double Arbuzov condensation of the di-benzylic bromide with bis(trimethylsilyloxy)phosphine, made from the reaction of ammonium hypophosphite and hexamethyldisilazane, provides the cyclic phosphinate ester (*J. Org. Chem. 60*:6076-81 (1995)) which can be converted to the phosphinic acid by saponification with NaOH or TMSBr. Alternatively, the di-benzyl bromide precursor can be obtained by bromination of a substituted 1,2-dimethyl benzene with bromine or N-bromosuccinimide (*J. Chem. Soc.* 3358-61 (1959)) or direct bromomethylation by reacting formaldehyde and HBr in presence of acetic acid (*J. Phys. Chem. 108(4)*:5145-55 (2004)).

[0496] Cyclic phosphonates can be synthesized by condensing a di-benzylic alcohol with trimethylphosphite (*Bull. Acad. Sci. USSR Div. Chem. Sci. 37*:1810-14 (1988)) to get the cyclic phosphite which is then converted to the cyclic phosphonate by a photo-Arbuzov rearrangement (*J. Organomet. Chem. 646*:239-46 (2002)). Alternatively, the cyclic phosphite can be obtained by condensing a di-benzylic alcohol with HMPT (*J. Org. Chem.* 57(10):2812-18 (1992)) or diethylphosphoramidous dichloride to get a cyclic phosphoramidous diester which is then converted to the cyclic phosphite by reaction with an alcohol, such as methanol or phenol, in the presence of an activating agent such as tetrazole or methylthio-tetrazole (*J. Org. Chem.*

61:7996-97 (1996)). The phosphonic acid is then obtained by selective monosaponification.

Synthesis of prodrugs of phosphinic acids and phosphonate monoesters

[0497] Prodrugs can be introduced at different stages of the synthesis. Most often these prodrugs are made from the phosphonic acid monoesters and phosphinic acids because of their lability.

[0498] Phosphinic acids and phosphonic acid monoesters can be alkylated with electrophiles such as alkyl halides and alkyl sulfonates under nucleophilic substitution conditions to give phosphonate esters. For example, compounds of Formula I wherein YR^{11} is an acyloxyalkyl group can be prepared by direct alkylation of compounds of Formula I with an appropriate acyloxyalkyl halide (*e.g.,* Cl, Br, I; *Phosphorus Sulfur 54*:143 (1990); *Synthesis* 62 (1988)) in the presence of a suitable base (*e.g.,* pyridine, TEA, diisopropylethylamine) in suitable solvents such as DMF (*J. Med. Chem. 37*:1875 (1994)). The carboxylate component of these acyloxyalkyl halides includes but is not limited to acetate, propionate, isobutyrate, pivalate, benzoate, carbonate and other carboxylates.

[0499] Dimethylformamide dialkyl acetals can also be used for the alkylation of phosphinic acids and phosphonic acid monoesters (*Collect. Czech Chem. Commu. 59*:1853 (1994)). Compounds of Formula I wherein YR^{11} is a cyclic carbonate, a lactone or a phthalidyl group can also be synthesized by direct alkylation of the free phosphonic acids with appropriate halides in the presence of a suitable base such as NaH or diisopropylethylamine (*J. Med. Chem. 38*:1372 (1995); *J. Med. Chem. 37*:1857 (1994); *J. Pharm. Sci. 76*:180 (1987)).

[0500] Alternatively, these phosphinate and monoester phosphonate prodrugs can be synthesized by the reactions of the corresponding chlorophospho(i)nate and an alcohol (*Collect Czech Chem. Commun. 59*:1853 (1994)). For example, a chlorophospho(i)nate is reacted with substituted phenols and arylalkyl alcohols in the presence of a base such as pyridine or TEA to give the compounds of Formula I wherein YR^{11} is an aryl group (*J. Med. Chem.*

39:4109 (1996); *J. Med. Chem. 38*:1372 (1995); *J. Med. Chem. 37*:498 (1994)) or an arylalkyl group (*J. Chem. Soc. Perkin Trans. 1 38*:2345 (1992)). The disulfide-containing prodrugs (*Antiviral Res. 22*:155 (1993)) can be prepared from a chlorophospho(i)nate and 2-hydroxyethyldisulfide under standard conditions. Chlorophospho(i)nates are also useful for the preparation of various phospho(i)namides as prodrugs. For example, treatment of a chlorophospho(i)nate with ammonia gives the phospho(i)namide.

[0501] Such reactive dichlorophosphonates can be generated from the corresponding phosphinic acids and phosphonic acid monoesters with a chlorinating agent (*e.g.,* thionyl chloride, *J. Med. Chem.* 1857 (1994); oxalyl chloride, *Tetrahedron Lett. 31*:3261 (1990); phosphorous pentachloride, *Synthesis* 490 (1974)). Alternatively, a dichlorophosphonate can be generated from its corresponding silyl phosphinate ester or phosphonic acid monester (*Synth. Commu. 17*:1071 (1987)) or alkyl phosphinate esters (*Tetrahedron Lett. 24*:4405 (1983); *Bull. Soc. Chim. 130*:485 (1993)).

[0502] Chlorophospho(i)nates are also useful for the preparation of various phosphonamides as prodrugs. For example, treatment of a chlorophospho(i)nate with an amine (*e.g.* an amino acid alkyl ester such as L-alanine ethyl ester) in the presence of a suitable base (*e.g.* triethylamine, pyridine, etc.) gives the corresponding phosphor(i)namide. Direct couplings of phosphinic acids or phosphonic acid monoesters with an amine (*e.g.* an amino acid alkyl ester such as L-alanine ethyl ester) are also reported to give the corresponding amidate under Mukaiyama conditions (*J. Am. Chem. Soc. 94*:8528 (1972)).

[0503] The SATE (*S*-acetyl thioethyl) prodrugs can be synthesized by the coupling reaction of the phosphinic acids or phosphonic acid monoesters of Formula I and S-acyl-2-thioethanol in the presence of DCC, EDCI or PyBOP (*J. Med. Chem. 39*:1981 (1996)).

Preparation of Key Precursors

A. Preparation of Compounds with Substituents on the Ring

[0504] Starting material and key intermediates required for the synthesis of the compounds in this invention are either commercially available or prepared using an existing method in the literature or a modification of a known method. Syntheses of some of those compounds are described herein.

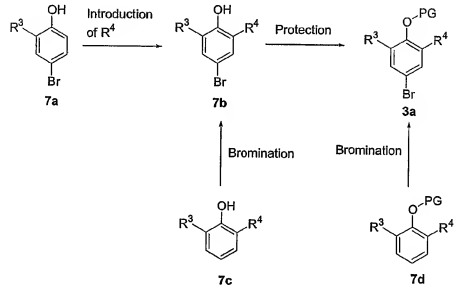
[0505] Precursor **2a** is prepared by reacting an anisole with iodine trifluoroacetate according to the reference procedures (*J. Med. Chem. 38*:695 (1995)). Anisoles with different R^3 and R^4 groups are either commercially available or can be prepared according to the literature procedures (*e.g., J. Med. Chem. 32*:320 (1989)).

[0506] Starting material **2b** is either commercially available or prepared according to known procedures. For example, compounds of **2b** wherein FG is NH_2-derived group can be prepared by reacting **3a** with benzophenone imine in the presence of a Pd catalyst such as $Pd_2(dba)_3$ or $Pd(OAc)_2$ (*Tetrahedron Lett. 38*:6367 (1997); *J. Am. Chem. Soc. 120*:827 (1998)). Compounds of **2b** wherein FG is S-derived group can be prepared by reacting a feasible 4-aminoanisole with $NaNO_2$ and potassium ethyl xanthate (*J. Am. Chem. Soc.* 68 (1946); *Heterocycles 26*:973 (1987)).

[0507] The useful precursor **3a** can either be commercially available reagents or prepared according to the existing methods. As described in Scheme 7, a simple protection of commercially available 4-bromophenol **7b** with different R^3 and R^4 groups according to the procedures known in the art leads to **3a**. Compound 3a can also be prepared by bromination of protected phenol **7d** (*J. Org. Chem. 53*:5545 (1988); *J. Org. Chem. 59*:4473 (1994); *Synthesis-Stuttgart 10*:868 (1986)). Introduction of various R^3 and R^4 groups to 4-bromophenol **7a** can be carried out to give **7b** which leads to **7a** after protection (*Tetrahedron Lett. 36*:8453 (1995); *J. Heterocyclic Chem. 28*:1395 (1991); *J. Fluorine Chem. 40*:23 (1988); *Synthesis-Stuttgart 11*:1878 (1999); *Synthetic Commu. 16*:681 (1986)). **7b** can also be prepared by the

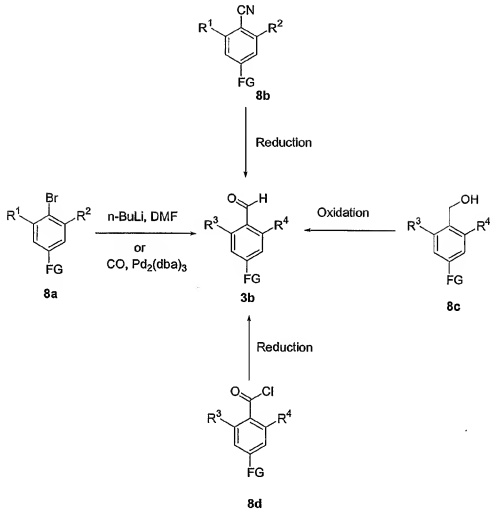
bromination of phenol **7c** (*J. Comb. Chem. 2*:434 (2000); *Chem. Soc. Jpn. 61*:2681 (1988); *Synthesis-Stuttgart 5*:467 (1992); *Org. Synth. 72*:95 (1993)).

Scheme 7



[0508] A number of methods are available for the preparation of the benzaldehyde **3b**. As illustrated in Scheme 8, bromobenzene **8a** can be converted to benzaldehyde **3b** by reacting with DMF (*Aust. J. Chem. 51*:177 (1998); *Bioorg. Med. Chem. Lett. 10*:2607 (2000)) or carbon monoxide in the presence of a palladium catalyst (*Bull. Chem. Soc. Jpn 67*:2329 (1994)). **3b** may be formed by oxidation of benzyl alcohol **8c** using common methods such as MnO_2 oxidation, PCC oxidation, Swern oxidation and Dess-Martin oxidation. Reduction of benzonitrile **8b** and benzoyl chloride **8d** also produces benzaldehyde **3b** (*Org. Synth. 3*:551 (1995); *J. Org. Chem. 46*:602 (1981)).

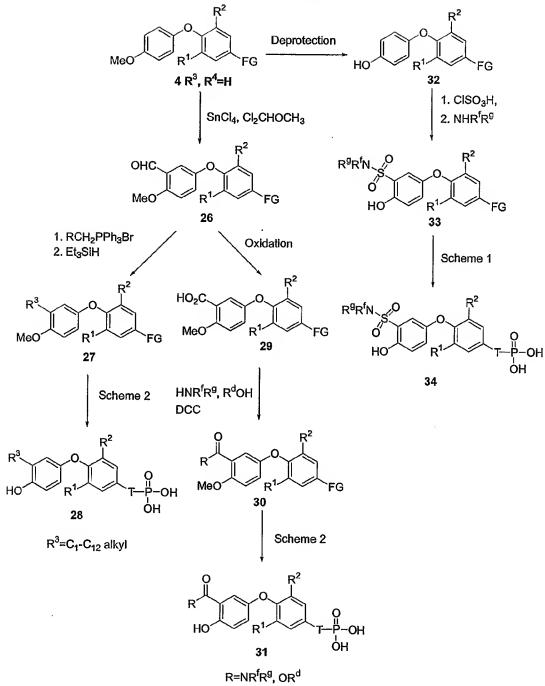
Scheme 8



[0509] For some of the compounds of Formula II-V, the R^3 and R^4 groups can be introduced after the biaryl ring backbone is installed. As illustrated in Scheme 9, the intermediate **4** (R^3, R^4=H) is converted to the benzylaldehyde **26** upon treatment with $SnCl_4$ and methoxymethyl dichloride. Various alkyl groups (C_1-C_{12}) are introduced by reacting the benzylaldehyde **26** with a Wittig reagent followed by the reduction of the resulting alkene with Et_3SiH to afford the intermediate **27** (*J. Med. Chem. 31*:37 (1988)). Also, benzylaldehyde **31** can be oxidized by $NaOCl_2$ to give the benzoic acid **29** (*Bioorg. Med. Chem. Lett. 13*:379 (2003)) which can be reacted with an

alcohol or amine under standard conditions to give the ester or amide **30**. Intermediates **27** and **30** can be converted to the corresponding phosphonic acids **28** and **33** following the same procedures as described in Scheme 2. In addition, deprotection of intermediate **4** provides the phenol **32** which can be converted to a variety of sulfonamides **33** upon treatment with $ClSO_3H$ and an amine. Phosphonic acids ($R^3 = S(=O)_2NR^fR^g$) can be formed following the same procedures as described in Scheme 1.

Scheme 9



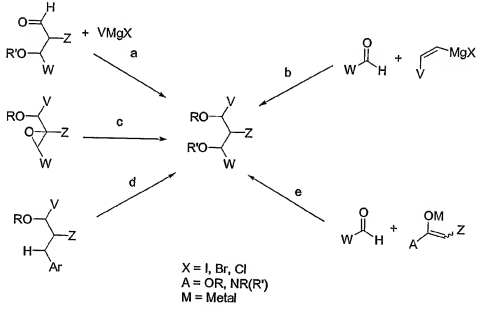
B. Preparation of 1,3-Diols

[0510] Various methods can be used to prepare 1,3-propanediols such as 1-substituted, 2-substituted, 1,2- or 1,3-annulated 1,3-propanediols.

1. 1-Substituted 1,3-propanediols

[0511] 1,3-Propanediols useful in the synthesis of compounds in the present invention can be prepared using various synthetic methods. As described in Scheme 10, additions of an aryl Grignard to a 1-hydroxy-propan-3-al give 1-aryl-substituted 1,3-propanediols (path a). This method is suitable for the conversion of various aryl halides to 1-arylsubstituted-1,3-propanediols (*J. Org. Chem. 53*:911 (1988)). Conversions of aryl halides to 1-substituted 1,3-propanediols can also be achieved using Heck reactions (*e.g.*, couplings with a 1,3-diox-4-ene) followed by reductions and subsequent hydrolysis reactions (*Tetrahedron Lett. 33*:6845 (1992)). Various aromatic aldehydes can also be converted to 1-substituted-1,3-propanediols using alkenyl Grignard addition reactions followed by hydroboration-oxidation reactions (path b).

Scheme 10



[0512] Aldol reactions between an enolate (*e.g.*, lithium, boron, tin enolates) of a carboxylic acid derivative (*e.g.*, tert-butyl acetate) and an aldehyde (*e.g.*, the Evans's aldol reactions) are especially useful for the asymmetric synthesis of enantioenriched 1,3-propanediols. For example, reaction of a metal enolate of *t*-butyl acetate with an aromatic aldehyde followed by reduction of the ester

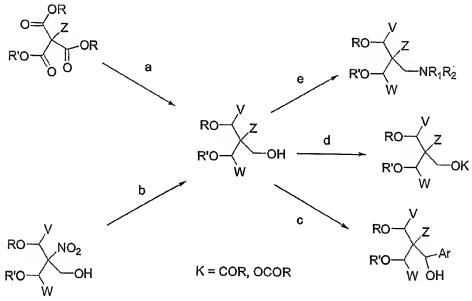
(path e) gives a 1,3-propanediol (*J. Org. Chem.* 55:4744 (1990)). Alternatively, epoxidation of cinnamyl alcohols using known methods (*e.g.*, Sharpless epoxidations and other asymmetric epoxidation reactions) followed by reduction reactions (*e.g.*, using Red-Al) give various 1,3-propanediols (path c). Enantioenriched 1,3-propanediols can be obtained via asymmetric reduction reactions (*e.g.*, enantioselective borane reductions) of 3-hydroxy-ketones (*Tetrahedron Lett.* 38:761 (1997)). Alternatively, resolution of racemic 1,3-propanediols using various methods (*e.g.*, enzymatic or chemical methods) can also give enantioenriched 1,3-propanediol. Propan-3-ols with a 1-heteroaryl substituent (*e.g.*, a pyridyl, a quinolinyl or an isoquinolinyl) can be oxygenated to give 1-substituted 1,3-propanediols using N-oxide formation reactions followed by a rearrangement reaction in acetic anhydride conditions (path d) (*Tetrahedron* 37:1871 (1981)).

2. 2-Substituted 1,3-propanediols

[0513] A variety of 2-substituted 1,3-propanediols useful for the synthesis of compounds of Formula I-VII can be prepared from various other 1,3-propanediols (*e.g.*, 2-(hydroxymethyl)-1,3-propanediols) using conventional chemistry (*Comprehensive Organic Transformations*, VCH, New York, 1989). For example, as described in Scheme 11, reductions of a trialkoxycarbonylmethane under known conditions give a triol via complete reduction (path a) or a bis(hydroxymethyl)acetic acid via selective hydrolysis of one of the ester groups followed by reduction of the remaining two other ester groups. Nitrotriols are also known to give triols via reductive elimination (path b) (*Synthesis* 8:742 (1987)). Furthermore, a 2-(hydroxymethyl)-1,3-propanediol can be converted to a mono acylated derivative (*e.g.*, acetyl, methoxycarbonyl) using an acyl chloride or an alkyl chloroformate (*e.g.*, acetyl chloride or methyl chloroformate) (path d) using known chemistry (*Protective Groups In Organic Synthesis* ; Wiley, New York, 1990). Other functional group manipulations can also be used to prepare 1,3-propanediols such as oxidation of one the hydroxymethyl groups in a 2-(hydroxymethyl)-1,3-propanediol to an aldehyde followed by addition

reactions with an aryl Grignard (path c). Aldehydes can also be converted to alkyl amines via reductive amination reactions (path e).

Scheme 11



3. Annulated 1,3-propane diols

[0514] Compounds of Formula I-VII wherein V and Z or V and W are connected by four carbons to form a ring can be prepared from a 1,3-cyclohexanediol. For example, *cis, cis*-1,3,5-cyclohexanetriol can be modified to give various other 1,3,5-cyclohexanetriols which are useful for the preparations of compounds of Formula I wherein R^{11} and R^{11} together are

wherein together V and W are connected via 3 atoms to form a cyclic group containing 6 carbon atoms substituted with a hydroxy group. It is envisioned that these modifications can be performed either before or after formation of a cyclic phosphonate 1,3-propanediol ester. Various 1,3-cyclohexanediols can also be prepared using Diels-Alder reactions (*e.g.*, using a pyrone as the diene:

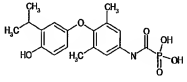
Tetrahedron Lett. 32:5295 (1991)). 2-Hydroxymethylcyclohexanols and 2-hydroxymethylcyclopentanols are useful for the preparations of compounds of Formula I wherein R^{11} and R^{11} together are

wherein together V and Z are connected via 2 or 3 atoms to form a cyclic group containing 5 or 6 carbon atoms. 1,3-Cyclohexanediol derivatives are also prepared via other cycloaddition reaction methodologies. For example, cycloadducts from the cycloadditon reactions of a nitrile oxide and an olefin can be converted to a 2-ketoethanol derivative which can be further converted to a 1,3-propanediol (including1,3-cyclohexanediol, 2-hydroxymethylcyclohexanol and 2-hydroxymethylcyclopentanol) using known chemistry (*J. Am. Chem. Soc. 107*:6023 (1985)). Alternatively, precursors to 1,3-cyclohexanediol can be made from quinic acid (*Tetrahedron Lett. 32*:547 (1991)).

Experimental

Example 1:

Compound 1: *N*-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxyphenoxy)] carbamoylphosphonic acid



Step a:

[0515] A mixture of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)aniline (*J. Med. Chem. 38*:695 (1995), 0.1 g, 0.35 mmol) and diphosgene (0.04 g, 0.19 mmol) in dioxane (3.0 mL) was heated at 60 °C

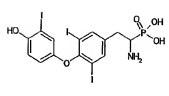
for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. To the residue was added a solution of diethyl phosphite (0.06 g, 0.42 mmol) in hexanes (1.0 mL with 3 drops of triethylamine) and the reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:3) to afford the diethyl phosphonate as an oil (0.1 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1 H), 7.17 (s, 2 H), 6.10-6.60 (m, 3 H), 4.10 (m, 4 H), 3.58 (s, 3 H), 3.07 (m, 1 H), 1.92 (s, 3 H), 1.93 (s, 3 H), 1.22 (m, 6 H), 0.99 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (3:1); R_f = 0.3.

Step b:

[0516] To a solution of diethyl *N*-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxy-phenoxy)] carbamoylphosphonate (0.1 g, 0.22 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C was added bromotrimethylsilane (0.30 mL, 2.2 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (2.0 mL) and the solution was cooled to -78 °C. Boron tribromide (1.3 mL, 1.3 mmol, 1.0 M in CH_2Cl_2) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by preparative LC-MS to afford the title compound as a yellow solid (0.035 g, 42%): mp 67-70 °C; Anal. Calcd for ($C_{18}H_{22}NO_6P$ + 0.2 H_2O + 0.3 CH_3OH): C, 55.99; H, 6.06; N, 3.57. Found: C, 55.79; H, 6.21; N, 3.39.

Example 2

Compound 2: 1-amino-2-[3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy) phenyl]ethylphosphonic acid



Step a:

[0517] To a solution of 4-benzyloxyphenylacetyl chloride (4.0 g, 16.2 mmol) in THF (10.0 mL) at room temperature was slowly added triethyl phosphite (3.33 mL, 19.5 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with hexanes (20 mL) and the mixture was filtered. White solid was collected and air-dried. The solid was dissolved in pyridine (25.0 mL) and hydroxylamine hydrochloride (1.96 g, 28 mmol) was added. The reaction mixture was stirred at room temperature for 72 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (7:3) to afford diethyl 2-(4-benzyloxyphenyl)-1-(hydroxyimino)ethylphosphonate as a colorless oil (5.2 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.38 (m, 7 H), 6.80 (d, J = 6.2 Hz, 2 H), 4.94 (s, 2 H), 3.80-4.10 (m, 4 H), 3.80 (s, 1 H), 3.76 (s, 1 H), 1.16 (t, J = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (2:3); R_f = 0.55.

Step b:

[0518] To a mixture of diethyl 2-(4-benzyloxyphenyl)-1-hydroxyiminoethylphosphonate (2.0 g, 5.3 mmol) and $NiCl_2$ (2.53 g, 10.6 mmol) in CH_3OH (40.0 mL) at room temperature was slowly added $NaBH_4$ (1.0 g, 26.4 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with 10% aqueous KOH (100 mL) and the mixture was extracted with ethyl ether (2x100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in THF (14.0 mL) and $(BOC)_2O$ (0.74 g, 3.4 mmol) was added. The reaction mixture was heated under reflux for 4 h and cooled to room temperature. The solvent

was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 4% CH_3OH in CH_2Cl_2 to afford diethyl 2-(4-benzyloxyphenyl)-1-(*tert*-butoxycarbonylamino) ethylphosphonate as an oil (1.12 g, 46%): ^1H NMR (300 MHz, CD_3OD): δ 7.38 (m, 5 H), 7.13 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 4.88 (s, 2 H), 4.12 (m, 5 H), 3.08 (m, 1 H), 2.70 (m, 1 H), 1.34 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = CH_3OH-CH_2Cl_2 (5:95); R_f = 0.45.

Step c:

[0519] A mixture of diethyl 2-(4-benzyloxyphenyl)-1-(*tert*-butoxycarbonylamino) ethylphosphonate (1.1 g, 2.4 mmol) and Pd-C (0.23 g, 10%) in CH_3OH (10 mL) was stirred under a H_2 atmosphere for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (15.0 mL). To the solution was added bis(pyridine)iodonium tetrafluoroborate (1.90 g, 5.1 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:1) to afford diethyl 1-(*tert*-butoxycarbonylamino)-2-(3,5-diiodo-4-hydroxyphenyl)ethylphosphonate as a yellow solid (1.30 g, 88%): ^1H NMR (300 MHz, CD_3OD): δ 7.67 (s, 2 H), 7.13 (d, J = 8.4 Hz, 1 H), 4.00-4.25 (m, 5 H), 3.00 (m, 1 H), 2.64 (m, 1 H), 1.38 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = CH_3OH-CH_2Cl_2 (5:95); R_f = 0.70.

Step d:

[0520] To a mixture of diethyl 1-(*tert*-butoxycarbonylamino)-2-(3,5-diiodo-4-hydroxyphenyl)ethylphosphonate (0.6 g, 0.96 mmol), 4-(*tert*-butyldimethylsilyloxy) phenylboronic acid (0.73 g, 2.89 mmol), copper acetate (0.21 g, 1.16 mmol) and 4A molecular sieves (1.20 g) in CH_2Cl_2 (8.0 mL) was added a solution of pyridine (0.4 mL, 4.8 mmol) and TEA (0.7 mL, 4.8 mmol). The reaction mixture was stirred at room temperature for 48 h, filtered

through a Celite plug and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:3) to afford diethyl 1-(*tert*-butoxycarbonylamino)-2-[4-(4'-(*tert*-butyldimethylsilyloxy)phenoxy)-3,5-diiodophenyl]ethylphosphonate as a white solid (0.48 g, 60%): ^{1}H NMR (300 MHz, CD_3OD): δ 7.64 (s, 2 H), 7.18 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.4 Hz, 1 H), 6.53 (d, J = 8.4 Hz, 1 H), 6.38 (d, J = 8.4 Hz, 1 H), 4.00 (m, 5 H), 2.90 (m, 1 H), 2.58 (m, 1 H), 1.20 (m, 6 H), 0.90 (m, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7); R_f = 0.60.

Step e:

[0521] To a mixture of diethyl 1-(*tert*-butoxycarbonylamino)-2-[4-(4-(*tert*-butyldimethylsilanyloxy)phenoxy)-3,5-diiodophenyl]ethylphosphonate (0.45 g, 0.54 mmol) in THF (6.0 mL) at 0 °C was added TBAF (0.81 mL, 0.81 mmol, 1.0 M in THF). The reaction mixture was stirred at room temperature for 20 min and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:1) to afford diethyl 1-(*tert*-butoxycarbonylamino)-2-[3,5-diiodo-4-(4'-hydroxyphenoxy)phenyl] ethylphosphonate as a white solid (0.24 g, 62%): ^{1}H NMR (300 MHz, CD_3OD): δ 7.74 (s, 2 H), 6.58 (d, J = 8.4 Hz, 2 H), 6.45 (d, J = 8.4 Hz, 2 H), 4.12 (m, 5 H), 3.08 (m, 1 H), 2.64 (m, 1 H), 1.32 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R_f = 0.40.

Step f:

[0522] A mixture of diethyl 1-(*tert*-butoxycarbonylamino)-2-[3,5-diiodo-4-(4'-hydroxyphenoxy) phenyl]ethylphosphonate (0.14g, 0.20 mmol) in 70% aqueous TFA (5.0 mL) was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was dissolved in C_2H_5OH (4.0 mL) and cooled to 0 °C. To the solution was added 40% aqueous methylamine (0.80 mL) followed by a solution of potassium iodide (0.16 g,

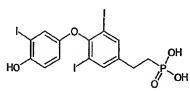
0.96 mmol) and iodine (0.06 g, 0.23 mmol) in H_2O (0.6 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with water and extracted with ethyl acetate (2x10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 4% CH_3OH in CH_2Cl_2 to afford diethyl 1-amino-2-[3,5-diiodo-4-(4'-hydroxy-3'-iodo-phenoxy)phenyl]ethylphosphonate as a yellow solid (0.10 g, 69%): ^1H NMR (300 MHz, CD_3OD): δ 7.85 (s, 2 H), 7.00 (d, J = 5.2 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.64 (dd, J = 3.2, 8.4 Hz, 1 H), 4.18 (m, 5 H), 3.08 (m, 1 H), 2.78 (m, 1 H), 1.36 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = CH_3OH-CH_2Cl_2 (5:95): R_f = 0.55.

Step g:

[0523] To a mixture of diethyl 1-amino-2-[3,5-diiodo-4-(4'-hydroxy-3'-iodo-phenoxy)phenyl]ethylphosphonate (0.05 g, 0.07 mmol) in CH_2Cl_2 (2.0 mL) at -78 °C was added bromotrimethylsilane (0.18 mL, 1.34 mmol). The reaction mixture was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The crude product was treated with CH_3CN-H_2O (5.0 mL, 9:1) and the solvent was removed under reduced pressure to afford 1-amino-2-[3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy) phenyl]ethylphosphonic acid as a yellow solid (0.044 g, 95%): mp 140 °C, dec; LC-MS m/z = 688 $[C_{14}H_{13}I_3NO_5P + H]^+$; Anal. Calcd for ($C_{14}H_{13}I_3NO_5P$ + 1.0 H_2O + 0.3 HBr): C, 23.06; H, 2.11; N, 1.92. Found: C, 22.74; H, 2.16; N, 1.67.

Example 3

Compound 3:
2-[3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy)phenyl]ethylphosphonic acid



Step a:

[0524] To a solution of tetraethyl methylenediphosphonate (1.6 g, 5.6 mmol) in THF (16.0 mL) at 0 °C was slowly added sodium hydride (0.14 g, 5.6 mmol). The reaction mixture was stirred at 0 °C for 30 min and a solution of 4-benzyloxybenzaldehyde (1.0 g, 4.7 mmol) in THF (4.0 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, quenched with H_2O (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford the phosphonate as white solid (1.5 g). The solid was dissolved in CH_3OH (15.0 mL) and Pd-C (0.40 g) was added. The reaction mixture was stirred under a H_2 atmosphere for 16 h, filtered through a Celite plug and concentrated under reduced pressure to afford diethyl 2-(4-hydroxyphenyl)ethylphosphonate as an oil (1.10 g, 91%): ^{1}H NMR (300 MHz, CD_3OD): δ 7.03 (d, J = 8.4 Hz, 2 H), 6.69 (d, J = 8.4 Hz, 2 H), 4.05 (m, 4 H), 2.77 (m, 2 H), 2.05 (m, 2 H), 1.30 (t, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1); R_f = 0.5.

Step b:

[0525] To a solution of diethyl 2-(4-hydroxyphenyl)ethylphosphonate (0.5 g, 1.9 mmol) in CH_2Cl_2 (12.0 mL) at room temperature was added bis(pyridine)iodonium tetrafluoroborate (1.6 g, 4.3 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:1) to afford diethyl 2-(3,5-diiodo-4-hydroxyphenyl)ethylphosphonate as a white solid (0.92 g, 90%): ^{1}H NMR (300 MHz, CD_3OD): δ 7.62 (s, 2 H), 4.05 (m, 4 H), 2.77 (m, 2 H), 2.05 (m, 2 H), 1.29 (t, J = 6.9 Hz, 6 H); TLC conditions:

Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R_f = 0.57.

Step c:

[0526] Diethyl 2-[3,5-diiodo-4-(4'-hydroxyphenoxy)phenyl]ethylphosphonate was synthesized from diethyl 2-(3,5-diiodo-4-hydroxyphenyl)ethylphosphonate (0.5 g, 0.98 mmol) by following the procedure described in example 2, step d followed by example 2, step e: white solid (0.15 g, 25%)^{1}H NMR (300 MHz, CD_3OD): δ 7.81 (s, 2 H), 6.68 (d, J = 8.4 Hz, 2 H), 6.53 (d, J = 8.4 Hz, 2 H), 4.07 (m, 4 H), 2.84 (m, 2 H), 2.16 (m, 2 H), 1.32 (t, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); phenol: R_f = 0.35.

Step d:

[0527] To a solution of diethyl 2-[3,5-diiodo-4-(4'-hydroxyphenoxy)phenyl] ethylphosphonate (0.15 g, 0.25 mmol) in ethanol (5.0 mL) at 0 oC was slowly added a solution of potassium iodide (0.19 g, 0.75 mmol) and iodine (0.07 g, 0.3 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O (10.0 mL) and extracted with ethyl acetate (15.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 2% CH_3OH in CH_2Cl_2 to afford diethyl 2-[3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy)phenyl]ethylphosphonate as a white solid (0.10 g, 56%): 1H NMR (300 MHz, CD3OD): δ 7.83 (s, 2 H), 6.96 (d, J = 5.4 Hz, 1 H), 6.73 (d, J = 8.4 Hz, 2 H), 6.62 (dd, J = 4.2, 8.4 Hz, 1 H), 4.08 (m, 4 H), 2.88 (m, 2 H), 2.18 (m, 2 H), 1.32 (t, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = CH3OH-CH2Cl2 (5:95), R_f = 0.50.

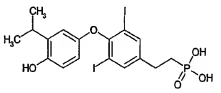
Step e:

[0528] To a solution of diethyl 2-[3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy)phenyl] ethylphosphonate (0.06 g, 0.08 mmol) in CH_2Cl_2 (1.5

mL) at 0 °C was slowly added bromotrimethylsilane (0.11 mL, 0.80 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with CH_3CN-H_2O (1:1, 5.0 mL) and the solvent was removed under reduced pressure to afford 2-[3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy)phenyl] ethylphosphonic acid as an off-white solid (0.05 g, 96%): mp 188 °C, dec; LC-MS m/z = 673 $[C_{14}H_{12}I_3O_5P + H]^+$; Anal. Calcd for ($C_{14}H_{12}I_3O_5P$ + 1.0 CH_3OH + 0.3 HBr): C, 24.45; H, 2.02; I, 53.45. Found: C, 24.79; H, 1.87; I, 53.36.

Example 4

Compound 4: 2-[3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy) phenyl]ethylphosphonic acid



Step a:

[0529] To a mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (0.30 g, 0.59 mmol, Yokoyama *et al. J. Med. Chem. 38*:695 (1995)) and copper (0.05 g, 0.78 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was slowly added a solution of diethyl 2-(3,5-diiodo-4-hydroxyphenyl)ethylphosphonate (0.2 g, 0.39 mmol) and TEA (0.10 mL, 0.66 mmol) in CH_2Cl_2 (0.6 mL). The reaction mixture was stirred at room temperature for 96 h, filtered through a Celite plug and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (2:3) to afford diethyl 2-[3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]ethylphosphonate as an off-white solid (0.25 g, 97%): ^1H NMR (300 MHz, CD_3OD): δ 7.82 (s, 2 H), 6.78 (d, J = 9.0 Hz, 1 H), 6.68 (d, J = 3.0 Hz, 1 H), 4.07 (m, 4 H), 3.30 (m, 1 H), 2.85 (m, 2 H), 2.18 (m, 2

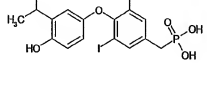
H), 1.30 (t, J = 6.9 Hz, 6 H), 1.15 (d, J = 7.2 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7); R_f = 0.64.

Step b:

[0530] To a solution of diethyl 2-[3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy) phenyl]ethylphosphonate (0.25 g, 0.38 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was slowly added bromotrimethylsilane (0.60 mL, 3.8 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (3.0mL) and cooled to -78 °C. Boron tribromide (1.80 mL, 1.80 mmol, 1.0 M CH_2Cl_2) was slowly added and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice (50 g) and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 2-[3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]ethylphosphonic acid as an off-white solid (0.20 g, 91%): mp 184-186 °C; LC-MS *m/z* = 589 $[C_{17}H_{19}I_2O_5P + H]^+$; Anal. Calcd for $C_{17}H_{19}I_2O_5P$: C, 34.72; H, 3.26. Found: C, 34.75; H, 3.12.

Example 5

Compound 5: 3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy) benzylphosphonic acid



Step a:

[0531] A mixture of 4-benzyloxybenzyl bromide (Chow *et al.*, *J. Org. Chem.* *62*:5116-27 (1997)) (1.0 g, 4.4 mmol) and triethyl phosphite (1.0 mL, 5.8 mmol) in DMF (2.8 mL) was heated at 155 °C for 4 h. The reaction mixture

was cooled to room temperature, quenched with H_2O (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (2:3) to afford the phosphonate as an oil (1.3 g). The phosphonate was dissolved in CH_3OH (12.0 mL) and Pd-C (10%, 0.33 g) was added. The reaction mixture was stirred under a H_2 atmosphere for 16 h, filtered through a Celite plug and concentrated under reduced pressure to afford diethyl 4-hydroxybenzylphosphonate as an oil (0.9 g, 84%): ^{1}H NMR (300 MHz, CD_3OD): δ 7.12 (d, J = 8.4 Hz, 2 H), 6.73 (d, J = 8.4 Hz, 2 H), 4.05 (m, 4 H), 3.16 (s, 1 H), 3.09 (s, 1 H), 1.26 (t, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R_f = 0.5.

Step b:

[0532] Diethyl 3,5-diiodo-4-hydroxybenzylphosphonate (0.85 g, 85%) was synthesized from diethyl 4-hydroxybenzylphosphonate (0.5 g, 2.1 mmol) by following the procedure described in example 3, step b: ^{1}H NMR (300 MHz, CD_3OD): δ 7.67 (d, J = 2.7 Hz, 2 H), 4.08 (m, 4 H), 3.15 (s, 1 H), 3.08 (s, 1 H), 1.28 (t, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (2:3); R_f = 0.6.

Step c:

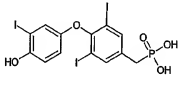
[0533] Diethyl 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy) benzylphosphonate (0.22 g, 88%) was synthesized from diethyl 3,5-diiodo-4-hydroxybenzylphosphonate (0.2 g, 0.4 mmol) by following the procedure described in example 4, step a: ^{1}H NMR (300 MHz, CD_3OD): δ 7.87 (d, J = 2.7 Hz, 2 H), 6.80 (d, J = 8.7 Hz, 1 H), 6.62 (d, J = 2.0 Hz, 1 H) 6.42 (dd, J = 3.3, 8.7 Hz, 1 H), 4.08 (m, 4 H), 3.78 (s, 3 H), 3.25 (m, 3 H), 1.32 (t, J = 6.9 Hz, 6 H), 1.14 (d, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (2:3); R_f = 0.6.

Step d:

[0534] 3,5-Diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzylphosphonic acid (0.18 g, 92%) was synthesized from diethyl 3,5-diiodo-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzylphosphonate (0.22 g, 0.34 mmol) by following the procedure described in example 4, step b: mp > 220 °C; LC-MS *m/z* = 575 $[C_{16}H_{17}I_2O_4P + H]^+$; Anal. Calcd for $(C_{16}H_{17}I_2O_5P+0.3 H_2O+0.5CH_3OH)$: C, 33.28; H, 3.32; I, 42.62. Found: C, 33.49; H, 3.23; I, 42.51.

Example 6

Compound 6: 3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy)benzylphosphonic acid



Step a:

[0535] Diethyl 3,5-diiodo-4-(4'-hydroxyphenoxy)benzylphosphonate (0.11 g, 17%) was obtained from diethyl 3,5-diiodo-4-hydroxybenzylphosphonate (0.55 g, 1.1 mmol) by following the procedure described in example 3, step c: ^{1}H NMR (300 MHz, CD_3OD): δ 7.87 (d, J = 2.7 Hz, 2 H), 6.70 (d, J = 8.7 Hz, 2 H), 6.54 (d, J = 2.0 Hz, 2 H) 4.10 (m, 4 H), 3.30 (s, 1 H), 3.22 (s, 1 H), 1.31 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R_f = 0.4.

Step b:

[0536] Diethyl 3,5-diiodo-4-(4'-hydroxy-3'-iodophenoxy)benzylphosphonate (0.08 g, 63%) was obtained from diethyl3,5-diiodo-4-(4'-hydroxyphenoxy)benzylphosphonate (0.1 g, 0.1 mmol) by following the procedure described in example 3, step d: ^{1}H NMR (300 MHz, CD_3OD): δ 7.87 (d, J = 2.4 Hz, 2 H), 6.92 (d, J = 6.4 Hz, 1 H), 6.74 (d, J = 8.7Hz, 1 H),

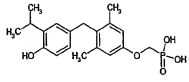
6.62 (dd, J = 2.4, 8.7 Hz, 1 H), 4.10 (m, 4 H), 3.30 (s, 1 H), 3.22 (s, 1 H), 1.31 (t, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = CH_3OH-CH_2Cl_2 (2:98); R_f = 0.6.

Step c:

[0537] 3,5-Diiodo-4-(4'-hydroxy-3'-iodophenoxy)benzylphosphonic acid (0.06 g, 90%) was obtained from diethyl 4-(4'-hydroxy-3'-iodophenoxy)-3,5-diiodobenzylphosphonate (0.08g, 0.1 mmol) by following the procedure described in example 3, step e: mp 168 °C, dec; LC-MS *m/z* = 659 $[C_{13}H_{10}I_3O_5P + H]^+$; Anal. Calcd for ($C_{13}H_{10}I_3O_5P$+1.6$H_2O$+ 0.5$CH_3OH$): C, 23.07; H, 2.18; I, 54.17. Found: C, 22.71; H, 1.80; I, 53.82.

Example 7

Compound 7: [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy] methylphosphonic acid



Step a:

[0538] To a stirring solution of NaH (0.855 g, 21.4 mmol) in DMF (40.0 mL) at 0 °C was added a solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol (5.60 g, 17.8 mmol), (Chiellini *et al., Bioorg. Med. Chem. Lett. 10*:2607 (2000)) in DMF (7.0 mL). The reaction mixture was stirred at room temperature for 1 h and cooled to 0° C. A solution of diethyl tosyloxymethylphosphonate (6.89 g, 21.4 mmol) in DMF (7.0 mL) was added. The reaction mixture was stirred at room temperature for 16 h, quenched with CH_3OH followed by dilution with water (100 mL) and extracted with ether (100 mLx2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

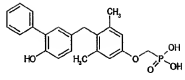
The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:3) to afford diethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate as a colorless oil (5.32 g, 64%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (d, J = 3.0 Hz, 1 H), 6.87 (d, J = 9.0 Hz, 1 H), 6.73 (s, 2 H), 6.58 (m, 1 H), 5.14 (s, 2 H), 4.36 (d, J = 9.0 Hz, 2 H), 4.10 (m, 4 H), 3.85 (s, 2 H), 3.36 (s, 3 H), 3.21 (m, 1 H), 2.17 (d, J = 6.0 Hz, 6 H), 1.25 (m, 6 H), 1.12-1.10 (d, J = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (1:1); R_f = 0.62.

Step b:

[0539] To a solution of diethyl 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propyl-benzyl)phenoxymethylphosphonate (5.32 g, 11.45 mmol) in dichloromethane (60.0 mL) at 0 °C was added bromotrimethylsilane (22.67 mL, 171.7 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile-water (1:1, 50 mL) and the solvent was removed under reduced pressure. The residue was treated with toluene and sonicated for 10 min. The mixture was filtered and washed with hexanes to afford [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid as a pink solid (4.00 g, 95%): mp 55-58 °C; LC-MS m/z = 365 $[C_{19}H_{25}O_5P + H]^+$; Anal. Calcd for ($C_{19}H_{25}O_5P$ + 0.5 H_2O + 0.2 CH_3OH): C, 60.72; H, 7.11. Found: C, 60.72, H, 7.18.

[0540] Using the appropriate starting material, compounds 7-1 to 7-21 were prepared in an analogous manner to that described for the synthesis of compound 7.

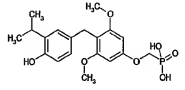
Compound 7-1: [3,5-dimethyl-4-(4'-hydroxy-3'-phenylbenzyl) phenoxy] methylphosphonic acid



[0541] Intermediate 3,5-dimethyl-4-(4'-methoxymethoxy-3'-phenylbenzyl) phenol was prepared from 2-phenylphenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0542] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.29 (s, 1 H), 6.60-7.60 (m, 8 H), 4.02 (d, J = 15 Hz, 2 H), 2.18 (s, 2 H); LC-MS m/z = 399 $[C_{29}H_{41}O_{11}P + H]^+$; Anal. Calcd for ($C_{29}H_{41}O_{11}P$ + 1.7 H_2O + 0.4 CH_3OH): C, 60.89; H, 6.39. Found: C, 60.53; H, 6.19.

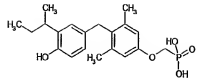
Compound 7-2: [3,5-dimethoxy-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy] methylphosphonic acid



[0543] Intermediate 3,5-dimethoxy-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol was prepared from 2,6-dimethoxy-4-hydroxybenzaldehyde according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0544] ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.86 (s, 1 H), 6.96 (d, J = 1.8 Hz, 1 H), 6.64 (dd, J = 1.8 Hz, J = 8.4 Hz, 1 H), 6.54 (d, J = 8.4 Hz, 1 H), 6.27 (s, 2 H), 4.07 (d, J = 10.2 Hz, 2 H), 3.74 (s, 6 H), 3.64 (s, 2 H), 3.08 (m, 1 H), 1.08 (d, J = 6.9 Hz, 6 H); LC-MS m/z = 397 $[C_{19}H_{25}O_7P + H]^+$; Anal Calcd for ($C_{19}H_{25}O_7P$ + 0.4 $CH_3CO_2C_2H_5$ + 0.9 H_2O): C, 55.25; H, 6.75. Found: C, 55.22; H, 7.13.

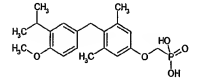
Compound 7-3: [3,5-dimethyl-4-(3'-*sec*-butyl-4'-hydroxybenzyl)phenoxy] methylphosphonic acid



[0545] Intermediate 3,5-dimethyl-4-(3'-*sec*-butyl-4'-methoxymethoxybenzyl) phenol was prepared from commercially available 2-*sec*-butylphenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0546] ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.92 (s, 1 H), 6.77 (s, 1 H), 6.68 (s, 2 H), 6.61 (d, J = 8.6 Hz, 1 H), 6.47 (d, J = 8.6 Hz, 1 H), 4.02 (d, J = 10.2 Hz, 2 H), 3.78 (s, 2 H), 2.90 (m, 1 H), 1.45 (q, J = 6.6 Hz, 2 H), 1.05 (d, J = 7.0 Hz, 3 H), 0.74 (t, J = 7.0 Hz, 3 H); LC-MS m/z = 379 $[C_{20}H_{27}O_5P + H]^+$; Anal Calcd for ($C_{20}H_{27}O_5P$ + 0.7 H_2O): C, 61.43; H, 7.32. Found: C, 61.22; H, 7.55.

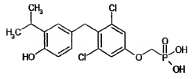
Compound 7-4: [3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxybenzyl)phenoxy] methylphosphonic acid



[0547] Intermediate 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxybenzyl)phenol was prepared from 2-*iso*-propylanisole according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0548] ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.99 (d, J = 2.1 Hz, 1 H), 6.88 (d, J = 8.4 Hz, 1 H), 6.76 (s, 2 H), 6.66 (m, 1 H), 4.09 (d, J = 10.2 Hz, 2 H), 3.91 (s, 2 H), 3.78 (s, 3 H), 3.23 (m, 1 H), 2.29 (s, 6 H), 1.16 (d, J = 7.2 Hz, 6 H); LC-MS m/z = 378 $[C_{20}H_{27}O_5P + H]^-$; Anal. Calcd for ($C_{20}H_{27}O_5P$ + 0.3 H_2O): C, 62.59; H, 7.25. Found: C, 62.37; H, 7.40.

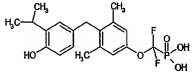
Compound 7-5: [3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy] methylphosphonic acid



[0549] Intermediate 3,5-dichloro-4-(3'-*sec*-butyl-4'-methoxymethoxybenzyl)phenol was prepared from 2,6-dichloro-4-benzyloxybenzaldehyde (*Organic Letters* **2002**, *4*, 2833) according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0550] mp.: 118 -120 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.01 (s, 2 H), 6.87 (d, J = 1.8 Hz, 1 H), 6.60 (dd, J = 3.0, 8.4 Hz, 1 H), 6.47 (d, J = 8.4 Hz, 1 H), 4.12 (d, J = 9.9 Hz, 2 H), 4.02 (s, 2 H), 3.20 - 3.10 (m, 1 H), 1.03 (d, J = 6.9 Hz, 6 H); LC-MS *m/z* = 405 $[C_{17}H_{19}Cl_2O_5P]^+$; Anal Calcd for: ($C_{17}H_{19}Cl_2O_5P$): C, 50.39, H, 4.73 Cl: 17.60. Found: C, 50.33, H, 5.03; Cl, 16.09.

Compound 7-6: difluoro-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl) phenoxy]methylphosphonic acid

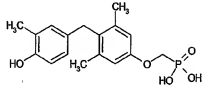


[0551] Intermediate 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol was prepared from 2-*iso*-propylphenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7 using diethyl bromodifluoromethylphosphonate.

[0552] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.02 (s, 1 H), 6.88 (m, 3 H), 6.65 (m, 1 H), 4.46 (m, 1 H), 3.84 (s, 3 H), 3.12 (s, 2 H), 3.12 (m, 1 H), 2.19 (s, 6 H), 1.12 (d, J = 6.0 Hz, 6 H); HPLC conditions: Column = 3 Chromolith SpeedRODs RP-18e, 100×4.6 mm; Mobile phase = Solvent A (Acetonitrile) =

HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M $NH_4H_2PO_4$/0.002 M $(NH_4)_2HPO_4$) with 5% acetonitrile. Flow rate = 4 mL/min; UV@ 255 nm. Retention time in minutes (rt = 5.68, 95% purity).

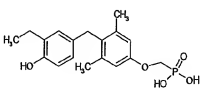
Compound 7-7: [3,5-dimethyl-4-[4'-hydroxy-3'-methylbenzyl]phenoxy] methylphosphonic acid



[0553] Intermediate 3,5-dimethyl-4-[3'-methyl-4'-methoxymethoxybenzyl]-phenol was prepared from 4-bromo-2-methyl-phenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0554] mp>230 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99(s, 1H), 6.68 – 6.525(m, 5H), 6.71(s, 2H), 4.03(d, 2H, J = 7.5 Hz), 3.77(s, 2H), 2.15(s, 6H), 2.02(s, 3H); LC- MS m/z = 335 [$C_{17}H_{21}O_5P$ – H]; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = isopropyl alcohol/water/ammonium hydroxide [7:2:1]; Rf = 0.23; Anal. Calcd for ($C_{17}H_{21}O_5P$ + 0.6 H_2O): C, 58.82; H, 6.45; Found: C, 58.73, H, 6.73.

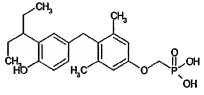
Compound 7-8: [3,5-dimethyl-4-[3'-ethyl-4'-hydroxybenzyl]phenoxy] methylphosphonic acid



[0555] Intermediate 3,5-dimethyl-4-[3'-ethyl-4'-methoxymethoxybenzyl]phenol was prepared from 4-bromo-2-ethyl-phenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7

[0556] ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96(s, 1H), 6.72 – 6.49(m, 5H), 4.03(d, 2H, J = 10.2 Hz), 3.78(s, 2H), 2.48(q, 2H, J = 8.1 Hz), 2.16(s, 6H), 1.06(t, 3H, J = 7.5 Hz); LC- MS m/z = 349 [$C_{18}H_{23}O_5P$ – H]; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = Isopropyl alcohol/ammonium hydroxide/water [7:2:1]; Rf = 0.20; Anal. Calcd for ($C_{17}H_{21}O_5P$ +1.3 H_2O + 0.3 CH_2Cl_2): C, 55.30; H, 6.59; Found: C, 55.36, H, 6.66.

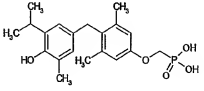
Compound 7-9: [3,5-dimethyl-4-[3'-(1-ethylpropyl)-4'-hydroxybenzyl] phenoxy]methylphosphonic acid



[0557] Intermediate 3,5-dimethyl-4-[3'-(1-ethylpropyl)-4'-methoxymethoxybenzyl]phenol was prepared from 2-(1-ethylpropyl)phenol (*J. Chem. Soc. Perkins Trans. 2:* 165 (1985)) according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7

[0558] mp: 60-64 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.84 (s, 1 H), 6.72 (s, 1 H), 6.67 (s, 2 H), 6.60 (m, 1 H), 6.46 (m, 1 H), 4.04 (d, J = 9.0 Hz, 2 H), 3.78 (s, 2 H), 2.74 (m, 1 H), 2.15 (s, 6 H), 1.49 (m, 4 H), 0.68 (m, 6 H); LC-MS m/z = 393 [$C_{21}H_{29}O_5P$ + H]$^+$; Anal. Calcd for ($C_{21}H_{29}O_5P$ + 0.5 H_2O + 0.2 $CH_3CO_2CH_2CH_3$): C, 62.48; H, 7.60. Found: C, 62.22; H, 7.83.

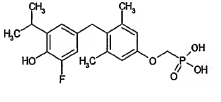
Compound 7-10: [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propyl-5'-methyl benzyl)phenoxy]methylphosphonic Acid



[0559] Intermediate 3,5-dimethyl-4-(3'-*iso*-propyl-5'-methyl-4'-methoxymethoxybenzyl)phenol was prepared from 2-*iso*-propyl-6-methylphenol (*J. Med. Chem. 12*:1350 (1980)) according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7

[0560] mp: 65-68 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 6.75 (s, 2 H), 6.69 (d, J = 2.1 Hz, 1 H), 6.49 (d, J = 2.1 Hz, 1 H), 4.22 (d, J = 10.2 Hz, 2 H), 3.89 (s, 2 H), 3.27 (m, 1 H), 2.23 (s, 6 H), 2.14 (s, 3 H), 1.15 (d, J = 7.2 Hz, 6 H); LC-MS m/z = 377 [$C_{20}H_{27}O_5P$ - H]$^+$; Anal. Calcd for ($C_{20}H_{27}O_5P$ + 1.0 H_2O): C, 60.60; H, 6.37. Found: C, 60.70; H, 7.75.

Compound 7-11: [3,5-dimethyl-4-(5'-fluoro-4'-hydroxy-3'-*iso*-propylbenzyl) phenoxy]methylphosphonic acid



Step a:

[0561] To a mixture of 4-bromo-2-fluoroanisole (2.0 g, 9.70 mmol) and 2-propanol (1.2 g, 19.4 mmol) at room temperature was added 80% H_2SO_4 (10.0 mL). The reaction mixture was heated at 80 °C for 12 h, cooled to room temperature, quenched with ice (50 g) and extracted with ether (20 mLx2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 5% ethyl acetate in hexanes to afford 4-bromo-6-fluoro-2-*iso*-propylanisole (0.92 g, 38 %): ^{1}H NMR (300 MHz, CD_3OD): δ 7.36 (d, J = 10.5 Hz, 1 H), 7.22 (d, J = 10.5 Hz , 1 H), 3.91 (s, 3 H), 3.24 (m, 1 H), 1.26 (d, J = 6.6 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (5:95); R_f = 0.50.

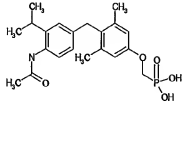
Step b:

[0562] To a solution of 4-bromo-6-fluoro-2-*iso*-propylanisole (0.92 g, 3.70 mmol) in CH_2Cl_2 (10.0 mL) at –78 °C was added BBr_3 (5.5 mL, 5.5 mmol, 1.0 M in CH_2Cl_2). After 5 min, the reaction mixture was stirred at room temperature for 16 h, poured into ice (50 g) and extracted with ethyl acetate (20.0 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford 4-bromo-6-fluoro-2-*iso*-propylphenol (0.90 g, 100%) as a dark oil, which was used for the next step without further purification: ^{1}H NMR (300 MHz, CD_3OD): δ 7.26 (d, J = 10.5 Hz, 1 H), 6.92 (d, J = 10.5 Hz , 1 H), 3.30 (m, 1 H), 1.23 (d, J = 6.6 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9); R_f = 0.40.

[0563] Intermediate 3,5-dimethyl-4-(5'-fluoro-3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol was prepared from 4-bromo-6-fluoro-2-*iso*-propylphenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7.

[0564] mp: 166-168 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 6.89 (d, J = 9.0 Hz, 1 H), 6.80 (s, 2 H), 6.03 (d, J = 9.0 Hz,1 H), 4.25 (d, J = 8.4 Hz, 2 H), 3.91 (s, 2 H), 3.34 (m, 1 H), 2.18 (s, 6 H), 1.30 (d, J = 6.9 Hz, 6 H); LC-MS m/z = 383 $[C_{19}H_{24}FO_5P + H]^+$; Anal Calcd for ($C_{19}H_{24}FO_5P$ + 0.6 H_2O): C, 58.04; H, 6.46. Found: C, 57.88; H, 6.46.

Compound 7-12: [4-(4'-acetylamino-3'-*iso*-propylbenzyl)-3,5-dimethyl phenoxy]methylphosphonic acid



Step a:

[0565] To a cooled solution of 2-*iso*-propyl aniline (714 mg, 5.28 mmol) in dichloromethane (20 mL) at –50 °C in a dry ice/acetone bath was added a solution of bromine (269 µl, 5.28 mmol) in dichloromethane (5 mL) over 20 min. After completion of the addition, the reaction mixture was stirred for an additional hour. Purification by column chromatography (silica gel, hexane/ethyl acetate) gave 4-bromo-2-*iso*-propyl-phenylamine as a brown oil (1.53 g, 57%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.01(m, 2H), 6.55(d, 1H, J = 13 Hz), 5.05(bs, 2H), 2.92(m, 1H), 1.11(d, 6H, J = 7 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = Hexane/ethyl acetate [10:1]; Rf = 0.11

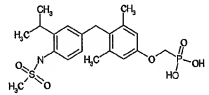
Step b:

[0566] A solution of 4-bromo-2-*iso*-propyl-phenylamine (780 mg, 3.64 mmol) in acetic anhydride (4 mL) was stirred at room temperature over night. The reaction was poured into water and the resulting white precipitate was filtered off and dried under vacuum to give *N*-(4-bromo-2-*iso*-propyl-phenyl)-acetamide as a light pink solid (0.770 g, 83%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.39(s, 1H), 7.43(d, 1H, J = 2.4 Hz), 3.16(m, 1H), 2.04(s, 3H), 1.13(d, 6H, J = 7 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = dichloromethane; Rf = 0.21

[0567] Intermediate 3,5-dimethyl-4-(5'-fluoro-3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol was prepared from *N*-(4-bromo-2-*iso*-propyl-phenyl)-acetamide according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7: mp>230 °C; LC- MS *m/z* = 404 [$C_{21}H_{28}NO_5P$ – H]; 1H NMR (300 MHz, DMSO-d_6): δ 9.23(s, 1H), 7.03(m, 2H), 6.71(s, 2H), 6.60(d, 1H, J = 9.3 Hz), 4.04(d, 2H, J = 9.3 Hz), 3.91(s, 2H), 2.17(s, 6H), 2.00(s, 3H), 1.06(d, 6H, J = 6.9 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = isopropyl alcohol/water/ammonium hydroxide [7:2:1]; Rf = 0.26; Anal. Calcd for

($C_{21}H_{28}NO_5P$ + 0.4 H_2O): C, 61.13; H, 7.03; N, 3.39 Found: C, 61.36, H, 7.22, N, 3.03.

Compound 7-13: [4-(3'-*iso*-propyl-4'-methanesulfonylaminobenzyl)-3,5-dimethyl phenoxy]methylphosphonic acid



Step a:

[0568] Intermediate *N*-[4-(4'-hydroxy-2',6'-dimethyl-benzyl)-2-*iso*-propyl-phenyl]-acetamide from the synthesis of compound 7-12 (320 mg, 0.68 mmol) was combined with HCl (10 mL) and water (2 mL) in a round bottom flask and heated at reflux over night. The solvent was removed under reduced pressure and the resulting solid was dissolved in a mixture of ethyl acetate (50 mL) and water (2 mL). The organic layer was removed and dried over sodium sulfate, filtered and concentrated under reduced pressure to give 4-(4'-amino-3'-*iso*-propylbenzyl)-3,5-dimethylphenol as a white powder (0.179 g, 98%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.934(s, 1H), 6.73(d, 1H, J = 1.8 Hz), 6.43(m, 5H), 4.58(bs, 2H), 3.69(s, 2H), 2.92(m, 1H), 2.10(s, 6H), 1.07(d, 6H, J = 6.6 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = Ethyl acetate; Rf = 0.69.

Step b:

[0569] To a solution of 4-(4'-amino-3'-*iso*-propylbenzyl)-3,5-dimethylphenol (80 mg, 0.30 mmol) in DMF (3 mL) was added sodium hydride (8.5 mg, 0.36 mmol) and the reaction was stirred for 10 min. at room temperature. Trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester was added and the reaction was stirred over night. An aqueous saturated solution of ammonium chloride (3 mL) was added and the resulting mixture was added to ethyl acetate (50 mL) and water (10 mL). The aqueous layer was removed and the ethyl acetate layer was washed 5 x with 10 mL water and 1 x with 10

mL brine. The ethyl acetate was dried over sodium sulfate, filtered and concentrated. The residue was purified by prep plate TLC using a 2000 μm silica gel plate eluted with ethyl acetate/ dichloromethane [3:1] to give diethyl [4-(4'-amino-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy]methylphosphonate (0.061 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.74(d, 1H, J = 1.8 Hz), 6.72(s, 2H), 6.45(dd, 1H, J = 14.4 Hz), 6.36(dd, 1H, J = 2 Hz, J = 7.5 Hz), 4.60(s, 2H), 4.35(d, 2H, J = 9.6 Hz), 4.11(m, 4H), 3.75(s, 2H), 2.90(m, 1H), 2.17(s, 6H), 1.25(t, 6H, J = 7 Hz), 1.07(d, 6H, J = 7.2 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = Ethyl acetate/Dichloromethane [1:1]; Rf = 0.54.

Step c:

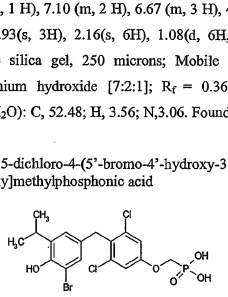
[0570] To a solution consisting of diethyl [4-(4'-amino-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy]methylphosphonate (43.6 mg, 0.104 mmol), in dichloromethane (2 mL) was added methane sulfonyl chloride (1 eq, 8 μl), and pyridine (1 eq, 8.4 μl). The reaction was stirred overnight at room temperature under an N_2 atmosphere (balloon). The solvent was removed under reduced pressure and the resulting residue was dissolved in ethyl acetate (25 mL) and washed 2 x with water (10 mL), 1x with 1N HCl (10 mL), and 1 x with brine (10 mL). The ethyl acetate was dried over sodium sulfate filtered and concentrated under reduced pressure giving pure diethyl [4-(3'-*iso*-propyl-4'-methanesulfonylaminobenzyl)-3,5-dimethylphenoxy]methylphosphonate (0.047 g, 97%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.94(s, 1H), 7.08(m, 2H), 6.76(s, 2H), 6.68(dd, 1H, J = 2.1 Hz, J = 8.7 Hz), 4.36(d, 2H, J = 10.2 Hz), 4.11(m, 4H), 3.39(m, 1H), 2.94(s, 3H), 2.23(s, 6H), 1.25(m, 6H), 1.08(d, 6H, J = 7 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = Ethyl acetate/Dichloromethane [1:1]; Rf = 0.36.

Step d:

[0571] To a solution consisting of diethyl [4-(3'-*iso*-propyl-4'-methanesulfonylaminobenzyl)-3,5-dimethylphenoxy]methylphosphonate (43.8 mg, 0.09 mmol) and dichloromethane (2 mL) was added HMDS (191 μl, 0.9

mmol) and TMSBr (191 µl, 0.9 mmol). The reaction was stirred over night at room temperature. The solvent was removed under reduced pressure and the resulting residue was co-evaporated 3 x with 2 mL dichloromethane. The resulting residue was taken up in 1N NaOH (2 mL) and washed 2 x with dichloromethane. The residual dichloromethane was removed under reduced pressure and the resulting aqueous layer was acidified with concentrated HCl. The resulting precipitate was filtered off and dried under vacuum to give the title compound as a light brown powder (0.022 g, 55%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.93 (s, 1 H), 7.10 (m, 2 H), 6.67 (m, 3 H), 4.02 (d, 2 H, J = 10 Hz), 3.91(s, 2H), 2.93(s, 3H), 2.16(s, 6H), 1.08(d, 6H, J = 7 Hz); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = Isopropyl alcohol/water/ammonium hydroxide [7:2:1]; R_f = 0.36; Anal. Calcd for ($C_{20}H_{28}O_6PS$ + 0.9 H_2O): C, 52.48; H, 3.56; N,3.06. Found: C, 52.49, H, 6.56, N, 3.23.

Compound 7-14: [3,5-dichloro-4-(5'-bromo-4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid



Step a:

[0572] To a mixture of diethyl [3,5- dichloro-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate (0.25 g, 0.49 mmol, intermediate for the synthesis of compound 7-5) in methanol (3.0 mL) at 0 °C was added 2 N HCl (1.0 mL). The reaction mixture was stirred at room temperature for 24 h, quenched with water (10.0 mL) and extracted with ethyl acetate (10.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 30% acetone in hexanes to afford diethyl [3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (0.17 g, 74%) as a colorless oil: ^{1}H

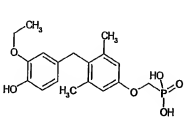
NMR (300 MHz, CD_3OD): δ 7.18 (s, 2 H), 7.00 (d, J = 2.4 Hz, 1 H), 6.75 (dd, J = 8.1, 2.4 Hz, 1 H), 6.62 (d, J = 8.1 Hz, 1 H), 4.48 (d, J = 10.5 Hz, 2 H), 4.25 (m, 4 H), 4.17 (s, 2 H), 3.25 (m, 1 H), 1.38 (t, J = 7.2 Hz, 6 H), 1.18 (d, J = 6.6 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (2:3); R_f = 0.70.

Step b:

[0573] To a mixture of diethyl [3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (0.16 g, 0.35 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added tetrabutylammonium tribromide (0.18 g, 0.38 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 30% acetone in hexanes to afford diethyl [3,5-dichloro-4-(5'-bromo-4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (0.12 g, 64%) as yellow oil: ^{1}H NMR (300 MHz, CD_3OD): δ 7.18 (s, 2 H), 7.02 (s, 2 H), 4.50 (d, J = 10.5 Hz, 2 H), 4.25 (m, 4 H), 4.18 (s, 2 H), 3.25 (m, 1 H), 1.38 (t, J = 7.2 Hz, 6 H), 1.18 (d, J = 6.6 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (2:3); R_f = 0.80.

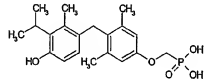
[0574] The title compound was prepared by the procedure described for the synthesis of compound 7, step b: mp: 188-190 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.18 (s, 2 H), 7.03 (s, 2 H), 4.32 (d, J = 10.2 Hz, 1 H), 4.18 (s, 2 H), 3.20-3.40 (m, 1 H), 1.19 (d, J = 7.2 Hz, 6 H); LC-MS m/z = 483 $[C_{20}H_{27}O_5P - H]^+$; Anal. Calcd for ($C_{17}H_{18}BrCl_2O_5P$ + 0.4 H_2O): C, 41.56; H, 3.86. Found: C, 41.44; H, 4.15.

Compound 7-15: [3,5-Dimethyl-4-[3'-ethoxy-4'-hydroxybenzyl]phenoxy] methylphosphonic acid



[0575] Intermediate 3,5-dimethyl-4-[3'-ethoxy-4'-methoxymethoxybenzyl]phenol was prepared from 4-bromo-2-ethoxy-phenol according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure used for the synthesis of compound 7: ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.62 (s, 1 H), 6.71 (s, 2 H), 6.65 (d, J = 8.1 Hz, 1 H), 6.59 (d, J = 1.5 Hz, 1 H), 6.27 (dd, J = 1.5, 8.1 Hz, 1 H), 4.04 (d, J = 10.2 Hz, 2 H), 3.93 (q, J = 6.9 Hz, 2 H), 3.82 (s, 2 H), 2.16 (s, 6 H), 1.29 (t, J = 6.9 Hz, 3 H); mp: shrinks at 145 °C; LC-MS m/z = 367 [$C_{18}H_{23}O_6P$ + H]$^+$; Anal Calcd for ($C_{18}H_{23}O_6P$ + 0.2MeOH + 0.4H_2O): C, 57.53; H, 6.53. Found: C, 57.39; H, 6.23.

Compound 7-16: [3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propyl-2'-methyl benzyl)phenoxy]methylphosphonic Acid



Step a:

[0576] To a solution of ethyl 2-methoxy-6-methylbenzoate (1.0 g, 5.1 mmol) in THF (15.0 mL) at –78 °C was added methylmagnesium bromide (3.78 mL, 11.32 mmol). After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was cooled to 0 °C, quenched with 1.0 M HCl and extracted with ether. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in hexanes to afford 2-(2-methoxy-6-methylphenyl)-2-propanol (0.60 g, 65 %) as colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.80 (dd, J = 12.0 Hz, 11.7 Hz, 1 H), 6.60 (d, J = 12.0 Hz, 1 H), 6.45 (d, J = 11.7 Hz, 1 H), 4.47 (s, 1 H), 3.52 (s, 3 H), 2.33 (s, 3 H), 1.33 (s, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5); R_f = 0.54.

Step b:

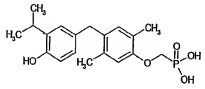
[0577] A solution of 2-(2-methoxy-6-methylphenyl)-2-propanol (0.50 g, 2.77 mmol) in ethyl acetate-acetic acid (9:1, 10 .0 mL) at room temperature was stirred under a H_2 atmosphere for 16 h. The mixture was filtered through a Celite plug and the solvent was removed under reduced pressure. The residue was dissolved in hexanes and washed with water. The organic layer was dried $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-*iso*-propyl-3-methylanisole (0.45 g, 100%) as colorless oil, which was used for the next step without further purification: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.01 (dd, J = 12.0 Hz, 11.7 Hz, 1 H), 6.78 (d, J = 12.0 Hz, 1 H), 6.70 (d, J = 11.7 Hz , 1 H), 3.74 (s, 3 H), 3.28 (m, 1 H), 2.26 (s, 3 H), 1.24 (d, J = 10.8 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9); R_f = 0.80.

Step c:

[0578] To a solution of 2-*iso*-propyl-3-methylanisole (0.44 g, 2.7 mmol) in CH_2Cl_2 at room temperature was added a solution of tetrabutylammonium tribromide (1.42g, 2.94 mmol) in CH_2Cl_2. The reaction mixture was stirred for 2 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 5% ethyl acetate in hexanes to afford 4-bromo-2-*iso*-propyl-3-methylanisole as yellowish oil (0.60g, 92%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.37 (d, J = 13.2 Hz, 1 H), 6.78 (d, J = 13.2 Hz , 1 H), 3.74 (s, 3 H), 3.38 (m, 1 H), 2.38 (s, 3 H), 1.25 (d, J = 10.8 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (5:95); R_f = 0.80.

[0579] The title compound was prepared from 4-bromo-2-*iso*-propyl-3-methylanisole according to the procedure described for the synthesis of compound 7-11: mp: 180-183 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 6.76 (s, 2 H), 6.34 (d, J = 8.4 Hz, 1 H), 6.03 (d, J = 8.4 Hz, 1 H), 4.22 (d, J = 10.5 Hz, 1 H), 3.81 (s, 2 H), 3.50 (m, 1 H), 2.37 (s, 3 H), 2.16 (s, 3 H), 1.39 (d, J = 6.9 Hz, 6 H); LC-MS m/z = 379 $[C_{20}H_{27}O_5P + H]^+$; Anal. Calcd for ($C_{20}H_{27}O_5P$+0.5 H_2O): C, 62.01; H, 7.28. Found: C, 61.98; H, 7.26.

Compound 7-17: [2,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy] methylphosphonic acid



Step a:

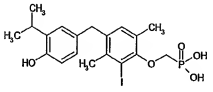
[0580] To a stirred suspension of 2,5-dimethyl phenol (5.0 g, 40.9 mmol) in H_2O (150 mL), at room temperature was added tetrabutylammonium tribromide (19.9 g, 41.39 mmol) in $CHCl_3$ (150 mL). The reaction mixture was stirred for 2 h at rt, the organic layer was separated and dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane-ethyl acetate (1:5) to afford 2,5-dimethyl-4-bromophenol as a brown solid (6.2 g, 76%); ^1H NMR (300 MHz, DMSO-d_6): δ 9.47 (s, 1 H), 7.24 (s, 1 H), 6.74 (s, 1 H), 2.21 (s, 3 H), 2.07 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (9:1); R_f = 0.52.

Step b:

[0581] Intermediate 2,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol was prepared from 2,5-dimethyl-4-bromo-*t*-butyldimethylsilyloxyphenol, and 3-*iso*-propyl-4-methoxymethoxybenzaldehyde according to the procedure described in (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* *10*:2607 (2000)) and transformed into the title compound by the procedure used for the synthesis of compound 7-13, step b followed by example 7, step b, (0.14 g, 90%); ^1H NMR (300 MHz, CD_3OD): δ 6.88 (d, J = 8.7 Hz, 2 H), 6.79 (s, 1 H), 6.64 - 6.72 (m, 2 H), 4.20 (d, J = 10.2 Hz, 2 H), 3.80 (s, 2 H), 3.10 - 3.15 (m, 1 H), 2.22 (s, 3 H), 2.20 (s, 3 H), 1.17 (d, J = 6.9 Hz, 6 H); LC-MS *m/z* = 365 $[C_{20}H_{25}O_6P + H]^+$; HPLC conditions: ODSAQ AQ-303-5 column; mobile phase = CH_3OH: 0.05%TFA (7:3) flow rate = 1.0 mL/min; detection = UV @ 254 nm retention

time in min: 10.96; Anal Calcd for ($C_{20}H_{25}O_6P$ + 0.3 H_2O): C, 61.84; H, 6.92. Found: C, 61.60; H, 6.72.

Compound 7-18: [2,5-Dimethyl-6-iodo-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid



Step a:

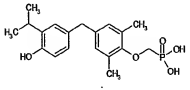
[0582] To a stirred solution of 2,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol (intermediate for the synthesis of compound 7-17; 0.35 g, 1.11 mmol) in EtOH (5.0 mL) and CH_3NH_2 40% in water (2.5 mL) was added iodine (0.34 g, 1.33 mmol) and KI (0.27 g 1.66 mmol) in H_2O (3 mL) at 0° C. The reaction mixture was stirred at 0 °C for 2 h, quenched with brine (50 mL) and extracted with ethyl acetate (100 mLx2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:3) to afford 2,5-dimethyl-6-iodo-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol as a colorless oil (0.32 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J = 2.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 6.88 (s, 1 H), 6.75 (dd, J = 2.4, 8.4 Hz, 1 H), 5.20 (s, 2 H), 3.95 (s, 2 H), 3.51 (s, 3 H), 3.35 - 3.30 (m, 1 H), 2.39 (s, 3 H), 2.30 (s, 3 H), 1.22 (d, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethylacetate (9:1); R_f = 0.6.

Step b:

[0583] The title compound was prepared from 6-iodo-3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol according to the procedure described for the synthesis of example 7-17, step b as white solid (0.15 g, 75%) mp 190 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 6.99 (s, 1 H), 6.92 (s, 1 H), 6.65 (s, 2 H), 4.16 (d, J = 10.5 Hz, 2 H), 3.94 (s, 2 H), 3.30 - 3.18 (m, 1 H),

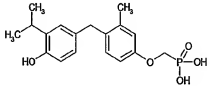
2.38 (s, 6 H), 1.18 (d, J = 6.9 Hz, 6 H); LC-MS m/z = 490 $[C_{19}H_{23}I_2O_5P+H]^+$; Anal Calcd for ($C_{20}H_{25}O_6P$ + 1.2 H_2O+1.0 $CHCl_3$): C, 38.05; H, 4.37. Found: C, 38.04; H, 4.33.

Compound 7-19: [2,6-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl) phenoxymethyl]phosphonic acid



[0584] Intermediate 2,6-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol was prepared from 3,5-dimethyl-4-hydroxy benzaldehyde and bromo-4-methoxymethoxy-3-*iso*-propylbenzene according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound according to the procedure described for the synthesis of compound 7-17, step b; (0.12 g, 85%); ^{1}H NMR (300 MHz, CD_3OD): δ 6.97 (s, 1 H), 6.83 (s, 2 H), 6.77 (d, J = 7.5 Hz, 1 H), 6.65 (d, J = 7.5 Hz, 1 H), 4.0 (d, J = 9.9 Hz, 2 H), 3.75(s, 2 H), 3.20 - 3.29 (m, 1 H), 2.28 (s, 6 H), 1.19 (d, J = 6.6 Hz, 6 H); LC-MS m/z = 363 $[C_{20}H_{25}O_6P$ -H$]^+$; (94%) HPLC conditions: ODSAQ AQ-303-5 column; mobile phase = CH_3OH: 0.05%TFA/H2O (7:3) flow rate = 1.0 mL/min; detection = UV @ 254 nm retention time in min: 10.92; Anal Calcd for ($C_{20}H_{25}O_6P$ + 1.2 H_2O): C, 59.12; H, 7.15. Found: C, 58.96; H, 6.77.

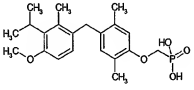
Compound 7-20: [4-(4'-hydroxy-3'-*iso*-propylbenzyl)-3-methyl-phenoxy]methylphosphonic Acid



[0585] Intermediate 4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)-3-methyl-phenol was prepared from 4-bromo-3-methyl-phenol (*J. Med. Chem. 12*:1350 (1980)) and 4-methoxymethoxy-3-*iso*-propylbenzaldehyde according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607

(2000) and transformed into the title compound by the procedure used for the synthesis of compound 7. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.04 (s, 1 H), 7.02-6.99 (d, J = 8.7 Hz, 1 H), 6.92 (s, 1 H), 6.81-6.76 (m, 2 H), 6.67 (s, 2 H), 4.03 (d, J = 10.5 Hz, 2 H), 3.76 (s, 2 H), 3.16-3.14 (m, 1 H), 2.19 (s, 3 H), 1.14-1.12 (d, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate; R_f = 0.11;

Compound 7-21: [2,5-Dimethyl-4-(4'-methoxy-2'-methyl-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid



Step a:

[0586] First step: To a stirring solution of 2,5-dimethyl-4-methoxybenzaldehyde (0.82 g, 5.0 mmol) at - 20 °C in CH_2Cl_2 (10 mL) was added BBr_3 (10 mL, 1M in CH_2Cl_2). The reaction mixture was stirred at room temperature for 16 hrs. It was added ice and diluted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1) to afford 2,5-dimethyl-4-hydroxy-benzaldehyde as a yellow solid (0.43 g, 57%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1 H), 9.99 (s, 1 H), 7.56 (s, 1 H), 6.69 (s, 1 H), 2.51 (s, 3 H), 2.14 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes; R_f = 0.48.

Step b:

[0587] To a stirring solution of 2,5-dimethyl-4-hydroxy-benzaldehyde (0.43 g, 2.86 mmol) in DMF (8 mL) at room temperature was added imidazole (0.43 g, 6.29 mmol) and chloro-triisopropyl-silane (0.74 mL, 3.43 mmol). The mixture was stirred at room temperature for 16 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and

water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:75) to afford 2,5-dimethyl-4-triisopropylsilanyloxy-benzaldehyde as a colorless oil (0.7 g, 80%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.07 (s, 1 H), 7.65 (s, 1 H), 6.69 (s, 1 H), 2.55 (s, 3 H), 2.21 (s, 3 H), 1.35 (m, 3 H), 1.10 (d, J = 6.9 Hz, 18 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 5% ethyl acetate in hexanes; R_f = 0.68.

[0588] Intermediate 2,5-dimethyl-4-(4'-methoxy-2'-methyl-3'-*iso*-propylbenzyl) phenol was prepared from 2,5-dimethyl-4-triisopropylsilanyloxy-benzaldehyde and 1-bromo-4-methoxy-2-methyl-3-*iso*-propylbenzene according to the procedure described in Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000) and transformed into the title compound by the procedure described for the synthesis of compound 7: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.93 (s, 1 H), 6.75 (d, J = 8.4 Hz, 1 H), 6.65 (d, J = 8.4 Hz, 1 H), 6.64 (s, 1 H), 4.09 (d, J = 9.9 Hz, 2 H), 3.79 (s, 2 H), 3.77 (s, 3 H), 3.34 (m, 1 H), 2.22 (s, 3 H), 2.20 (s, 3 H), 2.10 (s, 3 H), 1.31 (d, J = 7.2 Hz, 6 H); LC-MS m/z = 391 $[C21H29O5P - H]^-$.

Alternative method for the preparation of compound 7:

Step a:

[0589] A 3 neck 2 liter flask fitted with mechanical stirring, nitrogen bubbler, sodium hydroxide trap, and a cool water bath was charged with 2-*iso*-propyl phenol (157.8 g,1.1 mol) and dichloromethane (1000 ml). While maintaining the internal temperature at 15 °C to 20 °C, bromine (179.4 g, 1.1 mol) was added dropwise over 45 min. (The rate of addition is controlled so that the bromine color dissipates almost immediately). The reaction was complete by TLC (silica gel plates, 20% EtOAC/hexanes, R_f S.M. = 0.7, R_f product = 0.8). The flask was purged with nitrogen to remove most of the hydrogen bromide. The reaction mixture was then concentrated to an oil (252.0 g, 100%) which is pure enough to use in the next step. NMR: See Berthelot *et al.*, *Can J. Chem. 67*:2061 (1989).

Step b:

[0590] A 3 liter 3 neck round bottom flask equipped with mechanical stirring, temperature probe, cooling bath, and addition funnel with nitrogen inlet was charged with 4-bromo-2-*iso*-propylphenol (160 g, 0.75 mol) and methylene chloride (750 ml). While maintaining the temperature between 15 °C and 20 °C, a solution of diisopropylethylamine (146 g,1.13 mol) and chloromethyl methyl ether (66.4 g, 0.83 mol) in methylene chloride (100 ml) was added over 15 minutes. The solution was heated to reflux for 16 hours. The reaction was complete by TLC (silica gel plates, 10% EtOAC/hexanes, R_f S.M. = 0.5, R_f product = 0.9). After cooling to room temperature, the reaction was quenched by the addition of water (800 ml). After separation of layers, the aqueous phase was extracted with methylene chloride (500 ml). The combined organic layers were dried over $MgSO_4$, and then concentrated to an oil (204 g). The oil was purified by column chromatography (1.8 kg silica gel, 2.5% EtOAc/hexanes) to yield a clear oil (154 g, 79%). NMR See G. Chiellini et al. *Biorg. Med. Chem. Lett.* **2000**, *10*, 2607.

Alternative Step b

[0591] A 5 liter 4 neck indented round bottom flask equipped with a mechanical multi-paddle stirrer, and an addition funnel with nitrogen inlet was charged with 4-bromo-2-*iso*-propylphenol (100 g, 0.47 mol) and methylene chloride (2000 ml). Under high agitation, half of the P_2O_5 (75 g, 1.1 mol) was added. The reaction was stirred for one hour during which time dough balls formed. Additional P_2O_5 (75 g, 1.1 mol) was added and stirred for one hour. The reaction was complete by TLC (silica gel plates, 10% EtOAC/hexanes, R_f S.M. = 0.5, R_f product = 0.9). The reaction was carefully quenched by the addition of 10% K_2CO_3 (2000 ml). After separation of layers, the aqueous phase was extracted with methylene chloride (1000 ml). The combined organic layers were dried over $MgSO_4$, and then concentrated to an oil (116 g). The oil was purified by column chromatography (1.5 kg silica gel, 2.5% EtOAc/hexanes) to yield a clear oil (99.9 g, 83%).

Step c:

[0592] A 2 liter 3 neck round bottom flask equipped with mechanical stirring, cooling bath, temperature probe, and addition funnel with nitrogen inlet was charged with 4-bromo-3,5-dimethylphenol (90.0 g, 448 mmol), imidazole (90 g, 1.32 mol), and methylene chloride (900 ml). The solution was cooled to 10 °C. Triisopropylsilyl chloride (95.0 g, 493 mmol) was added over 10 minutes. The temperature rose to 20 °C. The solution became turbid, and a white precipitate formed. The reaction mixture was stirred at room temperature for 2.5 hours. The reaction was complete by TLC (silica gel plates, 10 % EtOAc/hexane, R_f S.M. = 0.3, R_f product = 0.9). Water (600 ml) was added and stirred for 20 minutes. After separation of layers, the organic phase was dried over $MgSO_4$ and concentrated to an oil (178 g) which is acceptable for use in the next step. The oil was purified by column chromatography (1.8 kg silica gel, 5 % EtOAc/hexane) to yield an oil (153 g, 96 %). NMR See Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000).

Step d:

[0593] A 3 liter 3 neck round bottom flask equipped with mechanical stirring, thermometer, cooling bath and 250 ml addition funnel was charged with 4-bromo-3,5-dimethylphenoxytriisopropylsilane (150 g, 420 mmol) and THF (1125 ml). The solution was cooled to –73 °C. While maintaining the temperature at less than or equal to –70 °C, 2.5 M n-butyllithium (252 ml, 630 mmol) was added over 1.5 hours. The solution was stirred at –73 °C for an additional 2.5 hours. While maintaining the temperature at less than or equal to –70 °C, a solution of dimethylformamide (61.3 g, 840 mmol) in THF (60 ml) was added over 35 minutes. After stirring for 30 minutes at –73 °C, TLC indicated that the reaction was complete (silica gel plates, 10 % EtOAc/hexane, R_f S.M. = 0.9, R_f product = 0.7). The reaction was warmed to room temperature, and then quenched by the addition of saturated ammonium chloride in water (1000 ml). After separation of layers, the aqueous phase was extracted with MTBE (250 ml). The combined organic layers were dried over

$MgSO_4$, and concentrated to an oil (125 g). The oil was purified by column chromatography (1.5 kg silica gel, 5 % EtOAc/hexanes) to yield an oil (113 g, 87 %). NMR See Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000).

Step e:

[0594] A 5 liter 3 neck round bottom flask equipped with a cooling bath, mechanical stirring, temperature probe, and addition funnel with nitrogen inlet was charged with bromo-4-methoxymethoxy-3-*iso*-propyl (136 g, 525 mmol) and THF (1300 ml). The solution was cooled to –75 °C. While maintaining the temperature at less than or equal to –70 °C, n-butyllithium solution (310 ml, 775 mmol) was added over 45 minutes. The solution was stirred at –75 °C for 1 hour. While maintaining the temperature at less than or equal to –70 °C, a solution of 2,6-dimethyl-4-triisopropylsilyloxybenzaldehyde (134 g, 438 mmol) in THF (200 ml) was added over 2 hours. The solution was stirred at –75 °C for 1 hour. TLC indicated that the reaction was complete (silica gel plates, 10 % EtOAc/hexane, R_f Bromide = 0.9, R_f Aldehyde = 0.7, R_f product = 0.2). After warming to room temperature, the reaction was quenched with saturated ammonium chloride in water (200 ml). After separation of layers, the aqueous phase was extracted with ethyl acetate (800 ml). The combined organic layers were washed with brine (700 ml), dried over $MgSO_4$, and concentrated to an oil (262 g). The oil was split into halves, and each half was purified by column chromatography (1.8 kg silica gel, 5 to 10 % EtOAc/hexane) to yield the product as a clear oil containing some EtOAc (148 g of product, 69 %). The fractions containing the product and an impurity were combined to give a clear oil (19.3 g). This was purified by column chromatography (400 g silica gel, 5 to 10 % EtOAc/hexanes) to give additional product as a clear oil (16.9 g, 7 %). NMR See Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000).

Step f:

[0595] A 2 liter round bottom flask equipped with magnetic stirring and a 3 way adapter was charged with (4-methoxymethoxy-3-*iso*-propylphenyl)-(2,6-

dimethyl-4-triisopropylsilyloxy)-methanol (72.1 g, 139 mmol), ethyl acetate (665 ml), acetic acid (35 ml), and 10 % Pd on Carbon (5.22 g). The flask was purged 3 times with nitrogen, and then a hydrogen balloon was attached to the adapter. After purging 3 times with hydrogen, the mixture was stirred at room temperature for 3 hours. The reaction was complete by TLC (silica gel plates, 10 % EtOAc/hexane, R_f S.M. = 0.2, R_f product = 0.9). After purging with nitrogen, the mixture was filtered through a small pad of Celite; rinsed with EtOAc (70 ml). The filtrate was washed with water (2 x 100 ml), and then by saturated $NaHCO_3$ in water until the wash was basic (4 x 100 ml). The organic layer was dried over $MgSO_4$ and then concentrated to an oil (62.5 g, 96 %). NMR See Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000).

Step g:

[0596] A 1 liter 1 neck round bottom flask equipped with magnetic stirring was charged with the 2,6-dimethyl-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)-4-triisopropylsilyloxybenzene (62.5 g, 133 mmol) and THF (600 ml). Tetraethylammonium fluoride hydrate (25.9 g, 174 mmol) was slightly ground in a beaker and then charged to the flask. The slurry was stirred at room temperature for 1 hour until TLC indicated that the reaction was complete (silica gel plates, 20 % EtOAc/hexane, R_f S.M. = 0.9, R_f product = 0.4). Water (300 ml) was added and stirred for 15 minutes. The mixture was diluted with MTBE (600 ml), and the layers were separated. The aqueous phase was extracted with MTBE (600 ml). The combined organic layers were washed with water (100 ml) followed by brine (200 ml). After drying over $MgSO_4$, the organic layer was concentrated to an oil (65 g). This was purified by column chromatography (1300 g silica gel, 10 to 20 % EtOAc/hexanes) to give the product as a clear oil (57.0 g, 95 %). NMR See Chiellini *et al.*, *Bioorg. Med. Chem. Lett. 10*:2607 (2000).

Step h:

[0597] A 5 liter 3 neck round bottom flask equipped with a cooling bath, mechanical stirring, temperature probe, and addition funnel with nitrogen inlet

was charged with 60% sodium hydride in mineral oil (10.62 g, 266 mmol). The sodium hydride was washed with hexanes (150 ml). Dimethylformamide (250 ml) was added, and the mixture cooled to 5°C. While maintaining the temperature < 10°C a solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)-phenol (55.53 g, 117 mmol) in DMF (150 ml) was added over 30 minutes. The solution was stirred at room temperature for 1 hour, and then cooled back to 5°C. While maintaining the temperature at less than or equal to 10 °C, a solution of the diethyl *p*-toluenesulfonyloxymethyl-phosphonate (86.93 g, 269 mmol) in DMF (150 ml) was added over 15 minutes. The solution was stirred at room temperature for 16 hours. The reaction was concentrated to a paste. The paste was treated with water (330 ml) and extracted with ethyl acetate (330 ml, 2x 250 ml). The combined organic layers were washed with brine (150 ml), dried over $MgSO_4$, and concentrated to an oil (116 g). The oil was purified by column chromatography (1.5 kg silica gel, 10 to 50 % EtOAc/hexane) to yield the product as a clear oil containing some EtOAc (54.76 g of product, 66 %). The fractions containing the product and diethyl p-toluenesulfonyloxymethyl were combined to give a clear oil (6.03 g). This was purified by column chromatography (120 g silica gel, 30 to 40 % EtOAc/hexanes) to give the product as a clear oil (3.74 g, 4 %). NMR see compound 7, step a.

Step i:

[0598] A 500 ml 3 neck round bottom flask equipped with magnetic stirring, temperature probe, addition funnel with a nitrogen inlet, and a cooling bath was charged with the diethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (19.61 g,42.2 mmol) and dichloromethane (200 ml). The solution was cooled to –30 °C. Trimethylsilyl bromide (64.96 g, 424 mmol) was added over 15 min. The bath was removed, and the solution stirred at room temperature for 16 hours. The reaction was concentrated on the rotary evaporator at 50 °C. The oil was then put on the vacuum pump for 30 minutes. The oil was dissolved in acetonitrile/water (110 ml/110 ml) and stirred at 50 °C for 30 min. The solution was concentrated to

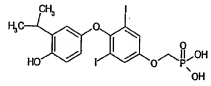
an oil. Acetonitrile (110 ml) was added, and the solution was concentrated to an oil. Methanol/toluene (30/190 ml) was added and the solution was concentrated to an oil. Methanol/toluene (30/190 ml) was added and the solution was concentrated to a foam. Toluene (220 ml) was added and the solution was concentrated to a solid. Toluene/hexane (190 ml/30 ml) was added, and the mixture was sonicated for 5 minutes. The solids were scraped down the sides of the flask, and the mixture was stirred at room temperature for 2 hours. The solids were collected by vacuum filtration and washed with hexane/toluene (2 ml/8 ml). The solids were dried overnight in the vacuum oven at 45 to 50 °C to yield the titled compound as an off-white solid (14.36 g). NMR see compound 7, step b.

Preparation of Diethyl p-toluenesulfonyloxymethylphosphonate

[0599] A 12 L, 3-neck round bottom flask was equipped with a mechanical stirrer, condenser, thermometer and heating mantle. The flask was flushed with nitrogen and charged with diethyl phosphite (554 g, 3.77 mol), paraformaldehyde (142 g, 4.72 mol), toluene (2 L) and triethylamine (53 mL, 5.76 mol). The mixture was stirred at 85-90 ° for 2 h, then at reflux for 1 h. The resulting yellow solution was cooled to 4 °C (ice bath) and p-toluenesulfonyl chloride (718 g, 3.77 mol) was added. The condenser was replaced with an addition funnel and triethylamine (750 mL) was added slowly with stirring, maintaining the temperature <10 °C. After the addition was complete (45 min.), the resulting mixture was stirred at ambient temperature for 14 h. The mixture was filtered and the filtercake was washed with toluene (2 X 250 mL). The combined filtrate and washings were washed with water (2 X 1 L, dried ($MgSO_4$, 200 g), filtered through Celite 521, and concentrated under reduced pressure to provide 1004 g of a cloudy yellow oil (77.6%). ^1H NMR ($CDCl_3$): NMR (DMSO): 7.82 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 4.36 (d, J = 9.6 Hz, 2H), 4.00 (m, 4H), 2.41 (s, 3H), 1.16 (m, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 40% EtOAc/hexanes, Rf = 0.24.

Example 8

Compound 8: [3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy) phenoxy]methylphosphonic acid



Step a:

[0600] To a solution of 4-benzoyloxyphenol (0.2 g, 0.93 mmol) in dichloromethane (9.3 mL) at 0 °C was added bis(pyridine)iodonium tetrafluoroborate (0.76 g, 2.06 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 4-benzoyloxy-3,5-diiodophenol as an off-white solid (0.22 g, 50%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (s, 1 H), 8.06 (m, 2 H), 7.72 (s, 2 H), 7.59 (m, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (4:1); R_f = 0.45.

Step b:

[0601] To a mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (0.77 g, 1.51 mmol) and copper powder (0.13 g, 2.01 mmol) in CH_2Cl_2 (4.4 mL) at 0 °C was added a solution of TEA (0.15 mL, 1.10 mmol) and 4-benzoyloxy-3,5-diiodophenol (0.47 g, 1.00 mmol) in dichloromethane (4.0 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl benzoate as an off-white solid (0.61 g, 98%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10 (m, 2 H), 7.96 (s, 2 H), 7.73 (m, 1 H), 7.60 (m, 2 H), 6.85 (d, J = 9.0 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.35 (m, 1 H), 3.74 (s, 3 H), 3.21 (m, 1 H), 1.13 (d, J = 6.0

Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (1:9); R_f = 0.42.

Step c:

[0602] A mixture of 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl benzoate (0.10 g, 0.16 mmol) and 1 N NaOH (0.81 mL, 0.81 mmol) in methanol (1.63 mL) was at room temperature for 24 h. The reaction mixture was neutralized with 2 N HCl, diluted with H_2O and extracted with CH_2Cl_2 (10 mLx2). The organic layers were concentrated under reduced pressure and the crude product was purified preparatory TLC with acetone-hexanes (1:4) as mobile phase to afford 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenol as an off-white solid (0.079 g, 95%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.99 (s, 1 H), 7.28 (s, 2 H), 6.81 (d, J = 12.0 Hz, 1 H), 6.67 (d, J = 3.0 Hz, 1 H), 6.30 (m, 1 H), 3.72 (s, 3 H), 3.18 (m, 1 H), 1.11 (d, J = 6.9 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (7:3); R_f = 0.42.

Step d:

[0603] To a stirred solution of 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenol (0.28 g, 0.55 mmol) in dichloromethane (17.0 mL) at –78 °C was added BBr_3 (13.1 mL, 13.1 mmol, 1.0 M solution in CH_2Cl_2). The reaction mixture was stirred at –78 °C for 10 min, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into ice and extracted with CH_2Cl_2 (20 mLx2). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (3:7) to afford 3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenol as an off-white solid (0.18 g, 66%): ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1 H), 8.91 (s, 1 H), 7.27 (s, 2 H), 6.62 (d, J = 9.0 Hz, 1 H), 6.56 (d, J = 3.0 Hz, 1 H), 6.18 (m, 1 H), 3.72 (s, 3 H), 3.14 (m, 1 H), 1.10 (d, J = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (7:3); R_f = 0.28.

Step e:

[0604] To a mixture of 3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenol (0.067 g, 0.14 mmol) and Cs_2CO_3 (0.220 g, 0.675 mmol) in DMF (1.35mL) at 0 °C was added trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester (0.040 g, 0.14 mmol). The reaction mixture was stirred at room temperature for 5 h, quenched with 1 N HCl and extracted with EtOAc (10 mLx2). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by preparatory TLC with acetone-hexane (2:3) as mobile phase to afford diethyl [3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonate as an off-white solid (0.048 g, 55%): ^1H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 1 H), 7.57 (s, 2 H), 6.63 (d, J = 9.0 Hz, 1 H), 6.56 (d, J = 3.0 Hz, 1 H), 6.19 (m, 1 H), 4.51 (d, J = 9.0 Hz, 2 H), 4.08 (m, 4 H), 3.14 (m, 1 H), 1.25 (m, 6 H), 1.10 (d, J = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (3:2); R_f = 0.29.

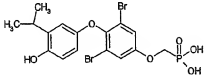
Step f:

[0605] To a solution of diethyl [3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy) phenoxy]methylphosphonate (0.14 g, 0.22 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added bromotrimethylsilane (0.28 mL, 2.20 mmol). The reaction mixture was stirred at room temperature 16 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile-water (1:1, 5.0 mL) and solvent was removed under reduced pressure. The crude product was treated methanol (10 mL) and the solvent was removed under reduced pressure to afford [3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonic acid as an off-white solid (0.080 g, 63%): mp 180 °C, dec; LC-MS m/z = 589 $[C_{16}H_{17}I_2O_6P - H]^-$; HPLC conditions: Column = 3 Chromolith SpeedRODs RP-18e, 100×4.6 mm; Mobile phase = Solvent A (Acetonitrile) = HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M $NH_4H_2PO_4$/0.002 M $(NH_4)_2HPO_4$) with 5% acetonitrile. Flow

rate = 4 mL/min; UV@ 255 nm. Retention time in minutes. (rt = 6.46, 97% purity).

[0606] Using the appropriate starting material, compounds 8-1 and 8-2 were prepared in an analogous manner to that described for the synthesis of compound 8.

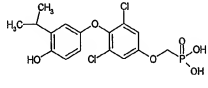
Compound 8-1: [3,5-dibromo-4-(3'-*iso*-propyl-4'-hydroxyphenoxy)phenoxy] methylphosphonic acid



[0607] Prepared from 4-benzoyloxy-3,5-dibromophenol according to the procedure described in compound 8.

[0608] mp: 77-80 °C; LC-MS *m/z* = 495,497 $[C_{16}H_{17}Br_2O_6P - H]^-$; ^1H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1 H), 7.42 (s, 2 H), 6.63 (m, 2 H), 6.22 (m, 1 H), 4.21 (d, J = 9.0 Hz, 2 H), 3.11 (m, 1 H), 1.10 (d, J = 6.0 Hz, 6 H); Anal. Calcd for ($C_{16}H_{17}Br_2O_6P$ + 0.2 C_6H_{14}): C, 40.06; H, 3.78. Found: C, 40.25, H, 3.89.

Compound 8-2: [3,5-dichloro-4-(3'-*iso*-propyl-4'-hydroxyphenoxy)phenoxy] methylphosphonic acid

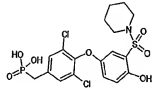


[0609] Prepared from 2,6-dichloro-4-(2-methoxyethoxy)phenol (*Synth. Commu.* **1997**, *27*, 107) according to the procedure described in compound 8.

[0610] mp: 73-76 °C; LC-MS *m/z* = 407 $[C_{16}H_{17}Cl_2O_6P - H]^-$; ^1H NMR (300 MHz, DMSO-d_6): δ 9.10 (s, 1 H), 7.34 (s, 2 H), 6.72 (m, 2 H), 6.32 (m, 1 H), 4.28 (d, J = 9.0 Hz, 2 H), 3.22 (m, 1 H), 1.17 (d, J = 6.0 Hz, 6 H); Anal. Calcd for ($C_{16}H_{17}Cl_2O_6P$ + 0.2 $C_4H_8O_2$ + 0.4 H_2O): C, 46.71; H, 4.53. Found: C, 46.95, H, 4.50.

Example 9

Compound 9: 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido) phenoxy]benzylphosphonic acid



Step a:

[0611] To a stirred solution of bis(4-methoxyphenyl)iodonium tetrafluoroborate (5.2 g, 13.5 mmol, N. Yokoyama *et al. J. Med. Chem.* **1995**, *38*, 695) and copper powder (1.14 g, 18.1 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added a solution of methyl 3,5-dichloro-4-hydroxybenzoate (39, 2.0 g, 9.0 mmol) and Et_3N (1.1 g, 1.5 mL, 12.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a Celite plug. The filtrate was washed with 2 N HCl (20 mL) and extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine and water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1: 9) to afford methyl 3,5-dichloro-4-(4'-methoxyphenoxy)benzoate as a white solid (1.59 g, 55%): mp 82-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 2 H), 6.85 (dd, J = 2.7, 4.8 Hz, 1 H), 6.80 (dd, J = 1.8, 4.5 Hz, 1 H), 6.78 (t, J = 3.3 Hz, 1 H), 6.74 (d, J = 2.4 Hz, 1 H), 3.94 (s, 3 H), 3.76 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:4); R_f = 0.7.

Step b:

[0612] To a stirred solution of methyl 3,5-dichloro-4-(4'-methoxyphenoxy)benzoate (1.5 g, 4.5 mmol) in CH_2Cl_2 (50 mL) at -78 °C was added BBr_3 (11. 4 mL, 11.4 mmol, 1 M solution in CH_2Cl_2). The reaction mixture was stirred at room temperature for 14 h,

poured into ice water (100 mL) and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was recrystallized from CH_2Cl_2, filtered and dried under reduced pressure to afford 3,5-dichloro-4-(4'-hydroxyphenoxy)benzoic acid as a brown solid (1.02 g, 75%): mp 163-165 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.02 (bs, 1 H), 8.0 (s, 2 H), 6.67 (m, 4 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); R_f = 0.3.

Step c:

[0613] To a stirred cold solution of CH_3OH (35 mL) and acetyl chloride (7 mL, 86.0 mmol) at 0 °C was added dropwise a solution of 3,5-dichloro-(4'-hydroxyphenoxy)benzoic acid (1.3 g, 4.3 mmol) in CH_3OH (5 mL). The reaction mixture was heated under reflux for 5 h and cooled to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The resulting solution was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was triturated with hexane-ether (8:2), filtered and dried under reduced pressure to afford methyl 3,5-dichloro-4-(4'-hydroxyphenoxy) benzoate as a brown solid (1.22 g, 90%): mp 152 -155 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 1 H), 8.08 (s, 2 H), 6.77 (t, J = 3.0 Hz, 1 H), 6.74 (t, J = 2.7 Hz, 1 H), 6.72 (t, J = 2.7Hz, 1 H), 6.68 (d, J = 2.7 Hz, 1 H), 3.87 (s, 3H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); R_f = 0.5.

Step d:

[0614] To a stirred solution of methyl 3,5-dichloro-4-(4'-hydroxyphenoxy)benzoate (1.2 g, 3.8 mmol) in $CHCl_3$ (10 mL) at 0 °C was added chlorosulfonic acid (3.9 mL, 38.3 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature. The reaction mixture was stirred for 2 h, poured into ice water and extracted

with ethyl acetate (3x100 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was used in the next step without purification. The crude product (1.1g, 2.6 mmol) was dissolved in THF (10 mL) and to it was added a solution of piperidine (0.68 g, 1 mL) in THF (5 mL). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:7) to afford desired methyl 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido) phenoxy]benzoate as a white solid (0.78 g, 60%): mp 122-125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1 H), 7.04 - 7.10 (m, 2 H), 6.85 (d, J = 2.7 Hz, 2 H), 3.96 (s, 3 H), 3.02 (t, J = 5.1 Hz, 4 H), 1.63 - 1.59 (m, 4 H), 1.50 - 1.40 (m, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:7); R_f = 0.35.

Step e:

[0615] To a stirred solution of methyl 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzoate (0.95 g, 2.0 mmol) in CH_2Cl_2 (15 mL) at –78 °C was added DIBAL-H (6.1 mL, 6.1 mmol, 1 M solution in CH_2Cl_2). The reaction mixture was stirred at room temperature for 5 h, cooled to 0 °C, quenched with saturated aqueous NaF solution (20 mL) and stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzyl alcohol as a white solid (0.66 g, 75%): mp 142 -145 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (s, 1 H), 7.40 (s, 2 H), 7.09 (dd, J = 3.0, 9.3 Hz, 1 H), 6.98 (dd, J = 3.0, 9.3Hz,

1 H), 6.84 (d, J = 2.4 Hz, 1 H), 4.70 (d, J = 3.9 Hz, 2 H), 3.02 (t, J = 2.4 Hz, 4 H), 1.70 - 1.50 (m, 4 H), 1.47 - 1.50 (m, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); R_f = 0.4.

Step f:

[0616] To a stirred solution of 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzyl alcohol (0.40 g, 0.92 mmol) in ethyl ether-DME (9:1, 10 mL) at 0 °C was added phosphorous tribromide (1.2 g, 0.5 mL, 4.64 mmol). The reaction mixture was stirred at 0 °C for 5 h, quenched with ice (10 g) and stirred at 0 °C for 30 min. The reaction mixture was extracted with ether (100 mL) and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzyl bromide as a colorless oil (0.34 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1 H), 7.42 (s, 2 H), 7.0 (dd, J = 3.0, 9.3 Hz, 1 H), 6.97 (d, J = 9.3 Hz, 1 H), 6.86 (d, J = 2.7 Hz, 1 H), 4.41 (s, 2 H), 3.02 (t, J = 5.1 Hz, 4 H), 1.65 - 1.55 (m, 4 H), 1.50 - 1.45 (m, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:7); R_f = 0. 75.

Step g:

[0617] To a stirred a solution of 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzyl bromide (0.12 g, 0.25 mmol) in toluene (5 mL) at room temperature was added triethylphosphite (0.42 g, 2.5 mmol). The reaction mixture was heated at 130 °C for 8 h and cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzylphosphonate as a white solid (0.12 g, 90%): mp 132 -135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1 H), 7.33 (d, J = 2.7 Hz, 2 H), 7.05 (dd, J = 3.0, 9.3 Hz,1 H), 6.97 (d, J = 9.3 Hz, 1

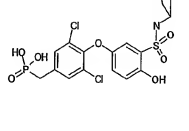
H), 6.83 (d, J = 3.3 Hz, 1 H), 4.09 (q, J = 6.9 Hz, 4 H), 3.07 (d, J = 21.6, 2 H), 3.02 (t, J = 6.0 Hz, 4 H), 1.67- 1.57 (m, 4 H), 1.50 - 1.42 (m, 2 H), 1.30 (t, J = 9.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1); R_f = 0.4.

Step h:

[0618] To a stirred solution of diethyl 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy]benzylphosphonate (0.1 g, 0.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TMSBr (0.27 g, 0.3 mL, 1.8 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_3OH (3 mL). The solvent was removed under reduced pressure. The residue was triturated with water (3 mL). The mixture was filtered and dried under reduced pressure to afford 3,5-dichloro-4-[4'-hydroxy-3'-(*N*-piperidinylsulfonamido)phenoxy)] benzylphosphonic acid as a white solid (0.07 g, 78%): mp 68 -72 °C; LC-MS m/z = 496 $[C_{18}H_{20}Cl_2NO_7PS+H]^+$; Anal Calcd for $(C_{20}H_{16}Cl_2FO_5P+0.5CH_2Cl_2)$: C, 41.28; H, 3.93; N, 2.60; S, 5.96. Found: C, 41.27; H, 3.86; N, 2.84; S, 5.84.

Example 10

Compound 10: 3,5-dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornyl sulfonamido)phenoxy]benzylphosphonic acid



Step a:

[0619] Methyl 3,5-dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido) phenoxy]benzoate was synthesized as a white solid

(0.89 g, 55%) from methyl-3,5-dichloro-4-(4'-hydroxy)phenoxybenzoate (1.3 g, 3.1 mmol) by following the procedure described in example 9, step d: mp 142 -145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1 H), 8.05 (s, 2 H), 7.06 (dd, J = 3.0, 8.7 Hz, 1 H), 6.98 (d, J = 9.3 Hz, 1 H), 6.92 (d, J = 3.0 Hz, 1 H), 4.53 (d, J = 7.5 Hz, 1 H), 3.95 (s, 3 H), 3.12 (m, 1 H), 2. 20 (bs, 1 H), 2.04 (bs, 1 H), 1.66 - 1.58 (m, 2 H), 1.46 - 1.40 (m, 2 H), 1.28 - 1.24 (m, 2 H), 1.20 - 1.16 (m, 1 H), 1.02 (dd, J = 1.8, 7.8 Hz, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); R_f = 0.3.

Step b:

[0620] 3,5-Dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido) phenoxy]benzyl alcohol was prepared as a white solid (0.46 g, 85%) from methyl 3,5-dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido)phenoxy]benzoate (0.5 g, 0.97 mmol) by following the procedure described in example 9, step e: mp 130 - 132 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (s, 2 H), 7.03 (dd, J = 3.3, 9.0 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 6.81 (d, J = 3.0 Hz, 1 H), 4.51 (s, 2 H), 2.90 (dd, J = 4.2, 8.1 Hz, 1 H), 2.06 (bs, 1 H), 1.86 (bs, 1 H), 1.37 (dd, J = 10.2, 24.3 Hz, 2 H), 1.30 - 1.22 (m, 2 H), 0.98 - 0.90 (m, 2 H), 0.85 - 0.79 (m, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); R_f = 0.3.

Step c:

[0621] 3,5-Dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido) phenoxy]benzyl bromide was prepared as a colorless oil (0.08 g, 75%) from 3,5-dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido)phenoxy]benzyl alcohol (0.1 g, 0.20 mmol) by following the procedure described in example 9, step f: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (s, 1 H), 7.34 (s, 2 H), 7.0 (dd, J = 3.0, 8.7 Hz, 1 H), 6.90 (d, J = 9.0 Hz, 1 H), 6.85 (d, J = 3.0 Hz, 1 H), 4.33 (s, 2 H), 3.05 (m, 1 H), 2.14 (bs, 1 H), 1.97 (bs, 1 H), 1.59 - 1.49 (m, 2 H), 1.38 - 1.32 (m, 2 H), 1.21 - 1.16 (m, 2 H), 1.12 - 1.06 (m, 1 H), 0.95 (dd, J = 1.8, 8.1 Hz, 1 H); TLC conditions:

Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); $R_f = 0.75$.

Step d:

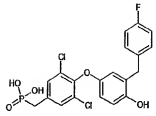
[0622] Diethyl-3,5-dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido)phenoxy]benzylphosphonate was prepared as a colorless oil (0.2 g, 83%) from 3,5-dichloro-4-[4'-hydroxy-3'-(*N-exo*-2-norbornylsulfonamido)phenoxy] benzyl bromide (0.22 g, 0.40 mmol) by following the procedure described in example 9, step g: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (s, 1 H), 7.33 (d, J = 2.7 Hz, 2 H), 7.09 (dd, J = 2.7, 8.7 Hz, 1 H), 6.97 (dd, J = 2.7, 9.0 Hz, 1 H), 6.88 (d, J = 3.0 Hz,1 H), 4.75 (d, J = 7.2 Hz, 1 H), 4.09 (q, J = 6.9 Hz, 2 H), 3.49 (s, 1 H), 3.14 (d, J = 21.6 Hz, 2 H), 3.11 - 3.05 (m, 1 H), 2.2 (bs, 1 H), 2.05 (d, J = 3.3 Hz, 1 H), 1.44 - 1.22 (m, 6 H), 1.20 - 1.15 (m, 1 H), 1.14 - 1.02 (m, 1 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); $R_f = 0.3$.

Step e:

[0623] 3,5-Dichloro-4-[3'-(*N-exo*-2-norbornylsulfonamido)-4'-hydroxyphenoxy]benzylphosphonic acid was prepared as a white solid (50 mg, 75%) from diethyl 3,5-dichloro-4-[3'-(*N-exo*-2-norbornylsulfonamido)-4'-hydroxyphenoxy]benzylphosphonate (0.075 g, 0.40 mmol) by following the procedure described in example 9, step h: mp 210 - 212 °C; LC-MS m/z = 522 $[C_{20}H_{22}Cl_2NO_7PS]^+$; Anal Calcd for $(C_{20}H_{22}Cl_2NO_7PS + 0.7\ CH_2Cl_2)$: C, 42.78; H, 4.06; N, 2.41. Found: C, 42.77; H, 4.17; N, 2.62.

Example 11

Compound 11: 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy] benzylphosphonic acid



Step a:

[0624] To a stirred solution of methyl 3,5-dichloro-(4'-hydroxyphenoxy)benzoate (0.5 g, 1.52 mmol) and *p*-fluorobenzoyl chloride (0.69 g, 0.45 mL 3.8 mmol) in CH_2Cl_2 (50 mL) at room temperature was added $TiCl_4$ (7.6 mL, 7.6 mmol, 1 M solution in CH_2Cl_2). The reaction mixture was stirred at room temperature for 8 days, quenched with saturated aqueous NH_4Cl (25 mL) and stirred for 2 h. The reaction mixture was extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with hexanes-ethyl ether (8:2), filtered and dried under reduced pressure to afford methyl 3,5-dichloro-4-[3'-(4-fluorobenzoyl)-4'-methoxyphenoxy]benzoate as a yellow solid. (0.39 g, 62%): mp 112 - 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 2 H), 7.81 (dd, J = 5.7, 9.0 Hz, 2 H), 7.09 (t, J = 8.4 Hz, 2 H), 6.93 (d, J = 2.7 Hz, 1 H), 6.92 (s, 1 H), 6.81 (d, J = 3.0 Hz, 1 H), 3.94 (s, 3 H), 3.69 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:4); R_f = 0.75.

Step b:

[0625] To a stirred solution of methyl 3,5-dichloro-4-[3'-(4-fluorobenzoyl)-4'-methoxyphenoxy]benzoate (350 mg, 0.78 mmol) and TFA (2 mL) in CH_2Cl_2 (50 mL) at room temperature was added triethylsilane (0.5 mL, 3.1 mmol). The reaction mixture was stirred at room temperature for 16 h, quenched with water (25 mL) and extracted with ether (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with hexanes, filtered and dried

under reduced pressure to afford methyl 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]benzoate as a brown solid (0.31 g, 92%): mp 108 -110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 2 H), 7.06 (dd, J = 6.0, 9.0 Hz, 2 H), 6.88 (t, J = 8.7 Hz, 2 H), 6.70 (d, J = 9.0 Hz, 1 H), 6.58 (d, J = 3.0 Hz,1 H), 6.48 (dd, J = 3.3, 9.0 Hz, 1 H), 3.89 (s, 3 H), 3.83 (s, 2 H), 3.71 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:8); R_f = 0.8.

Step c:

[0626] To a stirred suspension of $LiAlH_4$ (0.26 g, 6.95 mmol) in THF (40 mL) at 0 °C was slowly added a solution of methyl 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]benzoate (1.2 g, 2.76 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 20 h and cooled to 0 °C. The reaction mixture was quenched with 15% aqueous NaOH (1.5 mL), diluted with H_2O (3.0 mL) and stirred for 1 h. The reaction mixture was filtered through a Celite plug and the filtrate was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]benzyl alcohol as an oil (0.78 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 2 H), 7.16 (dd, J = 6.0, 8.7 Hz, 2 H), 7.04 (t, J = 8.7 Hz, 2 H), 6.84 (d, J = 9.0 Hz, 1 H), 6.67 (d, J = 3.0 Hz, 1 H), 6.45 (dd, J = 5.4, 9.3 Hz, 1 H), 5.45 (t, J = 5.7 Hz, 1 H), 4.48 (d, J = 5.7 Hz, 2 H), 3.82 (s, 2 H), 3.69 (s, 3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3); R_f = 0.45.

Step d:

[0627] To a stirred solution of 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy] benzyl alcohol (0.53 g, 1.29 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added BBr_3 (0.82 g, 3.2 mmol). The reaction mixture was stirred at room temperature for 16 h, poured into ice water (100

mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluted with ethyl acetate-hexanes (1:4) to afford 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy] benzyl bromide as a colorless oil (0.4 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 2 H), 7.14 (dd, J = 5.4, 8.7 Hz, 2 H), 6.95 (t, J = 8.7 Hz, 2 H), 6.66 (d, J = 9.0 Hz, 1 H), 6.62 (d, J = 2.7 Hz, 1 H), 6.53 (dd, J = 3.0, 8.7 Hz, 1 H), 4.04 (s, 2 H), 3.90 (s, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:4); R_f = 0.8.

Step e:

[0628] To a stirred solution of 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy] benzyl bromide (0.25 g, 0.55 mmol) in toluene (5 mL) at room temperature was added triethylphosphite (0.91 g, 5.5 mmol). The reaction mixture was heated at 120 °C for 8 h and cooled to room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy]benzylphosphonate as a colorless oil (0.2 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 2.7 Hz, 2 H), 7.15 (dd, J = 5.4, 9.0 Hz, 2 H), 6.95 (t, J = 8.7 Hz, 2 H), 6.66 (d, J = 4.8 Hz, 1 H), 6.65 (s, 1 H), 6.46 (dd, J = 3. 0, 8.7 Hz, 1 H), 4.07 (q, J = 7.2 Hz, 4 H), 3.89 (s, 2 H), 3.04 (d, J = 21.3 Hz, 2 H), 1.27 (t, J = 7.2 Hz,3 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1); R_f = 0.3.

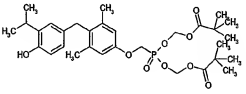
Step f:

[0629] To a stirred solution of diethyl 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy]benzyl phosphonate (0.09 g, 0.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TMSBr (0.28 g, 0.3 mL). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature. The reaction

mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in CH_3OH (5 mL) and the solvent was removed under reduced pressure. The residue was triturated with water (3 mL), filtered and dried under reduced pressure to afford 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy]benzylphosphonic acid as a white solid (0.075 g, 94%): mp 207-210 °C; LC-MS *m/z* = 457 $[C_{20}H_{16}Cl_2FO_5P+ H]^+$; Anal Calcd for ($C_{20}H_{16}Cl_2FO_5P$ + 0.8 CH_2Cl_2): C, 47.78; H, 3.39. Found: C, 47.78; H, 3.39.

Example 12

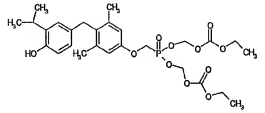
Compound 12-1: di(pivaloyloxymethyl) [3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate



[0630] To a mixture of [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-phenoxy] methylphosphonic acid (0.2 g, 0.5 mmol) and *N,N*-diisopropylethylamine (0.57 mL, 3.0 mmol) in CH_3CN (5.0 mL) at 0 °C was added pivaloyloxymethyl iodide (0.6 mL, 3.0mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:3) to afford the title compound as a white solid (0.22 g, 76%): ^1H NMR (300 MHz, CD_3OD): δ 6.79 (d, *J* = 3.0 Hz, 1 H), 6.68 (s, 2 H), 6.45-6.60 (m, 2 H), 5.75 (m, 4 H), 4.44 (d, *J* = 9.9 Hz, 2 H), 3.88 (s, 2 H), 3.20 (m, 1 H), 2.20 (s, 6 H), 1.20 (s, 18 H), 1.12 (d, *J* = 7.2 Hz, 6 H); LC-MS *m/z* = 593 $[C_{31}H_{45}O_9P + H]^+$; Anal. Calcd for ($C_{31}H_{45}O_9P$+0.3 H_2O): C, 62.26; H, 7.69. Found: C, 62.15; H, 7.77.

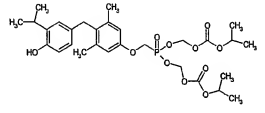
[0631] Using the appropriate starting material, compounds 12-2 and 12-9 were prepared in an analogous manner to that described for the synthesis of compound 12-1.

Compound 12-2: di(ethoxycarbonyloxymethyl)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy] methylphosphonate:



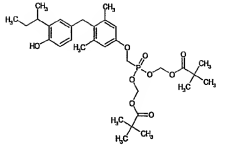
[0632] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.01 (s, 1 H), 6.86 (s, 1 H), 6.73 (s, 2 H), 6.63-6.61 (m, 1 H), 6.47-6.45 (m, 1 H), 5.72 (s, 2 H), 5.68 (s, 2 H), 4.51-4.48 (d, J = 7.5 Hz, 2 H), 4.17-4.12 (m, 4 H), 3.82 (s, 2 H), 3.13 (m, 1 H), 2.18-2.16 (m, 6 H), 1.23-1.18 (m, 6 H), 1.12-1.10 (d, J = 6.0 Hz, 6 H); LC-MS m/z = 569 $[C_{27}H_{37}O_{11}P + H]^+$; Anal. Calcd for ($C_{27}H_{37}O_{11}P$): C, 57.04; H, 6.56. Found: C, 56.60, H, 6.14.

Compound 12-3: di(isopropoxycarbonyloxymethyl)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate:



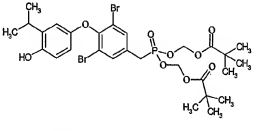
[0633] ^{1}H NMR (300 MHz, DMSO-d_6): δ8.97 (s, 1 H), 6.81 (s, 1 H), 6.69 (s, 2 H), 6.59-6.56 (m, 1 H), 6.43-6.40 (m, 1 H), 5.68 (s, 2 H), 5.63 (s, 2 H), 4.81-4.73 (m, 2 H), 4.46-4.43 (d, J = 7.5 Hz, 2 H), 3.78 (s, 2 H), 3.12-3.07 (m, 1 H), 2.14 (s, 6 H), 1.21-1.16 (m, 12 H), 1.08-1.06 (d, J = 6.0 Hz, 6 H); LC-MS m/z = 597 $[C_{29}H_{41}O_{11}P + H]^+$; Anal. Calcd for ($C_{29}H_{41}O_{11}P$): C, 58.38; H, 6.93. Found: C, 58.10, H, 7.54.

Compound 12-4: Di-(pivaloyloxymethyl)[3,5-dimethyl-4-(4'-hydroxy-3'-*sec*-butylbenzyl)phenoxy]methylphosphonate:



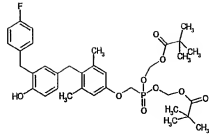
[0634] ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 1H), 6.76 (s, 1H), 6.72 (s, 2H), 6.64-6.61 (d, 1H), 6.65-6.47 (d, 1H), 5.73 (s, 2H), 5.68 (s, 2H), 4.48-4.45 (d, 2H), 3.81 (s, 2H), 2.93-2.90 (q, 1H), 2.17 (s, 6H), 1.52-1.44 (m, 2H), 1.17-1.11 (m, 18H), 1.08-1.06 (d, 3H), 0.78-0.73 (t, 3H); LC-MS *m/z* = 607.2 $[C_{32}H_{47}O_9P + H]^+$; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7); R_f = 0.56; Anal. Calcd for ($C_{32}H_{47}O_9P$ + 0.25 C_3H_6O): C, 63.32; H, 7.87. Found: C, 63.72; H, 8.19.

Compound 12-5: Di-(pivaloyloxymethyl)[3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzyl] phosphonate:



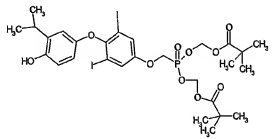
[0635] mp: 90-91 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.07 (s, 1H), 7.66 (s, 1H), 6.68-6.66 (m, 2H), 6.26-6.22 (d, 1H), 5.67-5.58 (q, 4H), 3.56-3.48 (d, 2H), 3.19-3.14 (m, 1H), 1.19-1.11 (m, 24H); LC-MS *m/z* = 709.4 $[C_{28}H_{37}Br_2O_9P + H]^+$; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7); R_f = 0.50; Anal. Calcd for ($C_{28}H_{37}Br_2O_9P$): C, 47.48; H, 5.26. Found: C, 47.09; H, 4.87.

Compound 12-6: Di-(pivaloyloxymethyl)[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxy-benzyl)phenoxy]methylphosphonate



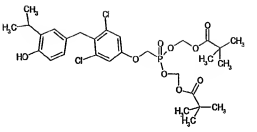
[0636] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17(1H, s), 7.18–7.02(m, 3H), 6.71-6.64 (m, 4H), 6.54 (m, 1H), 4.45 (d, 2H, J = 10Hz), 3.76 (s, 4H), 2.12 (s, 6H), 1.13 (s, 18H); LC-MS m/z = 633 $[C_{33}H_{44}O_9P + H]^+$; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate 50% in hexane; R_f = 0.48; Anal. Calcd for ($C_{33}H_{44}FO_9P$ +0.5 H_2O): C, 62.99; H, 6.90. Found: C, 62.99; H, 6.90.

Compound 12-7: Di(pivaloyloxymethyl)[3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonate



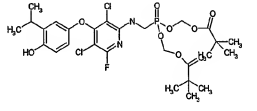
[0637] mp: 144-147 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1 H), 7.59 (s, 2 H), 6.68 (m, 1 H), 6.56 (m, 1 H), 6.25 (m, 1 H), 5.73 (d, J = 12.0 Hz, 2 H), 4.64 (d, J = 10.5 Hz, 2 H), 3.16 (m, 1 H), 1.17 (m, 18 H), 1.12 (d, J = 6.0 Hz, 6 H); LC-MS m/z = 819 $[C_{28}H_{37}O_{10}I_2P + H]^+$; HPLC conditions: Column = Agilent Zorbax SB-Aq RP-18 filter, 150×3.0; Mobile phase = Solvent A (Acetonitrile) = HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M $NH_4H_2PO_4$/0.002 M $(NH_4)_2HPO_4$). Flow rate = 1.0 mL/min; UV@ 255 nm. Retention time in minutes. (rt = 14.66/25.00, 93% purity); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1); R_f = 0.39.

Compound 12-8: Di(pivaloyloxymethyl)[3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate



[0638] ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.09 (s, 1 H), 7.21 (s, 2 H), 6.94 (s, 1 H), 6.64 (s, 2 H), 5.72 (d, J = 21.0 Hz, 2 H), 4.64 (d, J = 15 Hz, 2 H), 4.00 (s, 2 H), 3.15 (m, 1 H), 1.25 (m, 18 H), 1.11 (d, J = 4.5 Hz, 6 H); LC-MS m/z = 633 $[C_{29}H_{39}O_9Cl_2P + H]^+$; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:2); R_f = 0.62. Anal. Calcd for ($C_{29}H_{39}O_9Cl_2P$ + 0.3 H_2O + 0.2 $CH_3CO_2CH_2CH_3$): C, 54.49; H, 6.32. Found: C, 54.52, H, 6.33.

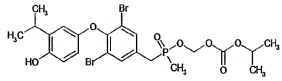
Compound 12-9: Di(pivaloyloxymethyl[4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-*iso*-propylphenoxy)-pyrid-2-ylamino]methylphosphonate



[0639] The title compound was prepared according to the procedure described for the synthesis of example 12 using [4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-*iso*-propylphenoxy)-pyrid-2-ylamino]methylphosphonic (US 6747048 B2):

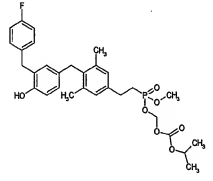
[0640] ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.20 (s, 1 H), 7.54 (t, J = 6.0 Hz, 1 H), 6.80 (d, J = 3.4 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 1 H), 6.44 (dd, J = 3.4, 8.8 Hz, 1 H), 5.62 (d, J = 12.4 Hz, 4 H), 3.97 (m, 2 H), 3.22 (m, 1 H), 1.07 – 1.17 (m, 24 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:2); R_f = 0.51; LC-MS m/z = 654 $[C27H36Cl2FN2O9P + H]^+$; Anal Calcd for (C27H36Cl2FN2O9P + 0.2Et_2OAc): C, 49.76; H, 5.65; N, 4.17. Found: C, 50.02; H, 6.02; N, 4.07.

Compound 12-10: Isopropyloxycarbonyloxymethyl [3,5-dibromo-4-(4'-hydroxy-3'- isopropylphenoxy)benzyl]methylphosphinite



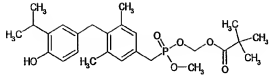
[0641] mp: 58-61 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.05 (s, 1H), 7.65 (d, J = 2.4 Hz , 2H), 6.67 (m, 2H), 6.23 (dd, J = 2.8, 10.2 Hz, 1H), 5.56 (d, J = 11.0 Hz , 2H), 4.80 (m, 1H), 3.36 (d, J = 10.2 Hz , 3H), 3.14 (m, 1H), 1.48 (d, J = 10.2 Hz, 3H), 1.25 (d, J = 6.8 Hz , 6H), 1.11 (d, J = 7.0 Hz, 6H); LC-MS m/z = 595 $[C_{22}H_{27}Br_2O_7P + H]^+$; Anal. Calcd for ($C_{17}H_{19}Br_2O_4P$): C, 44.47; H, 4.58. Found: C, 44.19; H, 4.80.

Compound 12-11: 2-[3,5-dimethyl-4-(3'-(4'-fluorobenzyl)-4'-hydroxybenzyl)phenyl]ethylphosphonic acid isopropoxycarbonyloxymethyl ester methyl ester



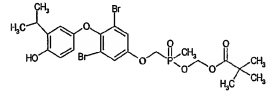
[0642] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17 (s, 1H), 6.88 – 7.22 (m, 4H), 6.88 (s, 2H), 6.71 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 2.1, 8.1 Hz, 1H), 5.55 (d, J = 12.9 Hz, 2H), 4.83 (m, 1H), 3.79 (s, 2H), 3.76 (s, 2H), 3.63 (d, J = 11.1 Hz, 3H), 2.65 (m, 2H), 2.12 (s, 6H), 2.05 (m, 2H), 1.22 (m, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (9:1); R_f = 0.42; LC-MS m/z = 559 $[C30H36FO7P + H]^+$; Anal Calcd for (C30H36FO7P): C, 64.51; H, 6.50. Found: C, 64.54; H, 6.26.

Compound 12-12: Pivaloxymethyl methyl 3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzylphosphonate



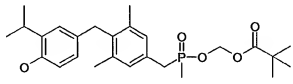
[0643] ^{1}H NMR (300 MHz, CD_3OD): δ 7.03 (d, J = 2.1 Hz, 2H), 6.83 (d, J = 2.1 Hz, 1H), 6.54 (m, 2H), 5.96 (m, 2H), 3.96 (s, 2H), 3.74 (d, J = 10.8 Hz, 3H), 3.25 (d, J = 21.0 Hz, 2H), 3.21 (m, 1H), 2.25 (s, 6H), 1.25 (s, 9H), 1.13 (d, J = 7.0 Hz, 6H); LC-MS m/z = 477 $[C_{26}H_{37}O_6P + H]^+$.

Compound 12-13: Pivaloyloxymethyl [3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxymethyl]methylphosphonate



[0644] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.04 (s, 1H), 7.50 (s, 2H), 6.66 (m, 2H), 6.30 (m, 1H), 5.69 (d, J = 13.5 Hz, 2H), 4.51 (d, J = 7.5 Hz, 3H), 3.17 (m, 1H), 1.68 (d, J = 15.0 Hz, 3H); 1.14 (m, 15H); LC-MS m/z = 608 $[C_{23}H_{29}Br_2O_7P + H]^+$.

Compound 12-14: Pivaloyloxymethyl[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinate



[0645] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 12, compound 12-1. ^{1}H NMR (300 MHz, CD_3OD): δ 7.02 (d, J = 2.4 Hz, 2H), 6.8 (s, 1H), 6.57-6.62 (m, 2H), 5.60-5.69 (m, 2H), 3.96 (s, 2H), 3.20 (m, 1H), 2.25 (s, 6H), 1.50 (d, J = 14.1 Hz, 3H), 1.20 (s, 9H), 1.13 (t, 6H); LC-MS m/z = 461 $[C_{26}H_{37}O_5P + H]^+$; Anal. Calcd for ($C_{26}H_{37}O_5P$+0.4 H_2O): C, 66.76; H, 8.15. Found: C, 66.85; H, 7.81; HPLC conditions: Column = Waters Atlantis; dC18-150×4.6